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VOLUME THE FIFTY-SIXTH.

COMPRISING THE REPORT OF THE PROCEEDINGS FOR THE SESSION 1904–1905.

Edited by Samuel G. Shattock.

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1905.

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TABLE OF CONTENTS

OF VOLUME LVI.

	PAGE
List of Presidents of the Society	iv
List of Officers and Members for 1905–1906	v
Annual Report of the Council for 1904-1905	xxix
List of Communications made during the Session 1904–1905	xxxi
List of Reports by Committees	xxxiii
List of Plates	xxxiv
List of Figures in the Text	xxxv
Communications	1
Index	389

Presidents of the Society.

ELECTED	
1846	CHARLES J. B. WILLIAMS, M.D., F.R.S.
1848	CHARLES ASTON KEY.
1850	PETER MERE LATHAM, M.D.
1852	CÆSAR H. HAWKINS, F.R.S.
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1855	JAMES MONCRIEFF ARNOTT, F.R.S.
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1869	Sir RICHARD QUAIN, Bart., M.D., LL.D., F.R.S.
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1885	JOHN SYER BRISTOWE, M.D., F.R.S.
1887	Sir JAMES PAGET, Bart., D.C.L., LL.D., F.R.S.
1889	WILLIAM HOWSHIP DICKINSON, M.D.
1891	Sir GEORGE MURRAY HUMPHRY, M.D., LL.D., F.R.S.
1893	FREDERICK WILLIAM PAVY, M.D., LL.D., F.R.S.
1895	HENRY TRENTHAM BUTLIN, D.C.L.
1897	JOSEPH FRANK PAYNE, M.D.
1899	WILLIAM WATSON CHEYNE, C.B., F.R.S.
1902	Sir JOHN BURDON SANDERSON, Bart., M.D., D.C.L., F.R.S.

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OF THE

Pathological Society of London,

ELECTED AT

THE GENERAL MEETING, MAY 16TH, 1905,

FOR THE SESSION 1905–1906.

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(1) Chairman of Section A. (2) Chairman of Section B.
(3) Chairman of Section C. (4) Chairman of Section D.

Committees.

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*** *Members are requested to inform the General Secretary of any change of address, etc., which may be necessary.*

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Honorary Members.

BOUCHARD, C., M.D., Professor of General Pathology, Paris.
CHAUVEAU, A., M.D., Professor of Physiology at the Medical School of Lyons.
KOCH, R., M.D., Director of the Institute for Infective Diseases, Berlin.
The Right Honourable Lord LISTER, F.R.S., F.R.C.S., 12, Park crescent, Portland place, W.
METCHNIKOFF, E., M.D., Chef de Service à l'Institut Pasteur, Paris.
ORTH, J., M.D., Professor of Pathological Anatomy in the University of Berlin.
VON RECKLINGHAUSEN, F. D., Director of the Pathological Institute, Strassburg.
RINDFLEISCH, E., M.D., Professor of Pathological Anatomy in the University of Bonn.
ROUX, P. P. E., M.D., Sous-directeur de l'Institut Pasteur, Paris.
SALOMONSEN, C. J., Professor of General Pathology and Bacteriology in the University of Copenhagen.
WELCH, W. H., M.D., Professor of Pathology, Johns Hopkins University, Baltimore.
WILKS, SIR SAMUEL, Bart., M.D., LL.D., F.R.S., F.R.C.P., 8, Prince Arthur Road, Hampstead, N.W.
ZIEGLER, E., M.D. Professor of Pathological Anatomy, Freiburg.

EXPLANATION OF ABBREVIATIONS.

P.—President.
T.—Treasurer.
V.-P.—Vice-President.
S.—Secretary.
C.—Member of Council.
E.—Editor of the 'Transactions.'

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1879 **ABERCROMBIE**, JOHN, M.D., 23, Upper Wimpole street, W. (C. 1897-1900.)

1896 ABRAHAMS, BERTRAM LOUIS, B.Sc., M.B., 14, Welbeck street, W.

1883 ACLAND, THEODORE DYKE, M.D., 19, Bryanston square, W. (C. 1892-4.)

1891 ADAMI, J. GEORGE, M.A., M.D., Montreal, Canada.

1890 ADAMS, JAMES, M.D., 4, Chiswick place, Eastbourne.

1848 **AIKIN**, CHARLES A., 12, Ladbroke terrace, W. (C. 1864-6.)

1872 AIKIN, CHARLES EDMUND, Llandrillo, Corwen, North Wales.

1897 ALCOCK, SAMUEL K., M.D., Portland House, Burslem.

1882 **ALLCHIN**, WILLIAM HENRY, M.D., 5, Chandos street, W.

1884 ANDERSON, ALEXANDER RICHARD, 5, East Circus street, Nottingham.

1897 ANDREWES, FREDERICK W., M.D., 31, Humpstead lane, Highgate, N. (C. 1900—. Com. Sect. B, 1901—.)

1902 ARMOUR, DONALD, M.B., 89, Harley street, W.

1883 ASHBY, HENRY, M.D., 13, St. John street, Manchester.

1863 BAGSHAWE, FREDERICK, M.A., M.D., 35, Warrior square, St. Leonard's-on-Sea.

1904 BAILEY, WILLIAM HENRY, M.D., Featherstone Hall, Southall, Middlesex.

1902 BAINBRIDGE, F. A., M.B., 1, Vernon Chambers, Southampton row, W.C.

1856 **Balding**, DANIEL BARLEY, Royston, Herts.

1881 BALLANCE, CHARLES A., M.S., 106, Harley street, W. (C. 1890-2. C. Com. Sect. C, 1901—4. S. 1899—1901.)

1875 BARKER, ARTHUR E. J., 87, Harley street, W. (C. 1884-6. V.P. 1896-7.)

1899 BARKER, A. J. G., Kuching, Sarawak, Borneo.

1885 BARLING, GILBERT, M.B., 87, Cornwall street, Newhall street, Birmingham. (C. 1894-7.)

1901 BARNARD, HAROLD L., M.S., 21, Wimpole street, W.

1874 **BARLOW**, Sir THOMAS, Bart., K.C.V.O., M.D., B.S., 10, Wimpole street, W. (C. 1879-81. V.-P. 1894-6.)

1899 BARRATT, JOHN OGLETHORPE WAKELIN, M.D., Lister Institute of Preventive Medicine, Chelsea, S.W.

1877 BARROW, A. BOYCE, 8, Upper Wimpole street, W.

1881 BARRS, ALFRED GEORGE, M.D., 22, Park place, Leeds.

1853 **BARWELL**, RICHARD, 55, Wimpole street, W. (C. 1862-4. V.-P. 1889-90.)

Elected

1861 **BASTIAN**, H. CHARLTON, M.A., M.D., F.R.S., 8A, Manchester square, W. (C. 1869-71. V.-P. 1885-7.)

1877 BATEMAN, ARTHUR W., B.A., Tenterfield, New South Wales.

1895 BATTEN, FREDERICK E., M.D., 33, Harley street, W. (C. Com. Sect. A, 1903–5.)

1876 **BATTESON**, JOHN, 188, Goldhawk road, Shepherd's Bush.

1882 BATTLE, WILLIAM HENRY, 49, Harley street, W. (C. 1898—1901.)

1902 BAUMANN, E. P., M.D., 38, Harley street, W.

1870 BÄUMLER, CHRISTIAN G. H., M.D., The University, Freiburg, in Baden Baden, Germany.

1874 BEACH, FLETCHER, M.B., 79, Wimpole street, W., and Winchester House, Kingston Hill, Surrey.

1892 BEADLES, CECIL F., Colney Hatch Lunatic Asylum, N. (C. 1898—1901.)

1879 BEALE, EDWIN CLIFFORD, M.B., 23, Upper Berkeley street, W.

1852 **BEALE**, LIONEL S., M.B., F.R.S., 6, Bentinck street, Manchester square, W. (C. 1858-9. V.-P. 1874-5.)

1856 BEALEY, ADAM, M.D., M.A., Felsham Lodge, Hollington park, St. Leonard's-on-Sea.

1900 BEATON, ROBERT MILNE, M.B., 97, Dartmouth park avenue, N.W.

1904 BEATTIE, JAMES M., M.D., Pathological Department, University of Edinburgh.

1897 BEDDARD, ARTHUR P., M.D., 44, Seymour street, W.

1865 BEEBY, WALTER, M.D., Rapollo, Liguria, Italy (Nov.—May), and Varallo, Valsesia (May, June, Sept., Oct.).

1880 **BEEVOR**, CHARLES EDWARD, M.D., 135, Harley street, W. (C. 1888-90.)

1883 BENHAM, R. FITZROY, 11, Earl's Court square, S.W.

1886 BENNETT, FREDERICK JOSEPH, 17, George street, Hanover square, W.

1877 BENNETT, Sir WILLIAM HENRY, K.C.V.O., 1, Chesterfield street, W. (C. 1891-3.)

1889 BENTLEY, ARTHUR, J. M., M.D., Mena House, Pyramids, Cairo, Egypt.

1878 BERNARD, FRANCIS R., M.D., Prawls, Stone, near Tenterden, Kent.

1904 BERNSTEIN, JULIUS M., M.B., Erskine Chambers, 36, Lincoln's Inn Fields, W.C.

1882 BERRIDGE, WILLIAM ALFRED, Redhill, Surrey.

1886 BERRY, JAMES, B.S., 21, Wimpole street, W. (C. 1895-7.)

1903 BEVERIDGE, WILFRID WILLIAM OGILVIE, M.B., R.A.M.C., D.S.O., 3, Wilhiaham Mansions, Sloane street, S.W.

1856 **Bickersteth**, EDWARD R., 2, Rodney street, Liverpool.

1882 BINDLEY, PHILIP HENRY, M.B. Address uncommunicated.

1865 BISSHOPP, JAMES, Mount Pleasant, Tunbridge Wells.

1889 BLACK, ROBERT, M.D., 14, Pavilion Parade, Brighton.

1863 BLANCHET, JEAN B., M.D., M.S., Montreal, Quebec, Canada.

1879 BOILEAU, J. P. H., M.D., Brigade-Surgeon, Army.

1900 BOKENHAM, THOMAS JESSOPP, 10, Devonshire street, Portland place, W.

1904 BOLTON, CHARLES, M.D., 16, Devonshire street, Portland place, W.

1900 BOLTON, JOSEPH SHAW, M.D., B.S., B.Sc., East Sussex County Asylum, Hellingly S.O., Sussex.

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1902 Bonney, W. F. Victor, M.D., M.S., 10, Devonshire street, Portland place, W.

1899 Bosanquet, W. Cecil, M.D., 117*a*, Harley street, W.

1869 Bourne, Walter, M.D. (Travelling).

1861 Bower, Richard Norris (Travelling).

1881 Bowlby, Anthony A., C.M.G., 24, Manchester square, W. (M.G.C. 1884—1900. C. 1886-8, 1895-7. S. 1893-5. V.-P. 1898—1900.)

1895 Box, Charles R., M.D., 2, Devonshire place, Portland Place, W.

1892 Boyce, Rubert William, M.S., F.R.S., Thompson Yates Laboratories, Liverpool University, Liverpool.

1904 Boycott, Arthur Pagin, B.Sc., M.B., B.Ch., Guy's Hospital, S.E.

1882 Boyd, Stanley, B.S., 134, Harley street, W. (C. 1893-6. V.-P. 1897-9.)

1889 Bradford, John Rose, M.D., F.R.S. 8, Manchester square, W. (C. 1897—1900. C. Com. Sect. C, 1902-5. S. 1900-2.)

1880 Bramwell, Byrom, M.D., 23, Drumsheugh Gardens West, Edinburgh.

1904 Branson, William P. S., M.B., 59, Gordon square, W.C.

1889 Bredin, J. Noble, The Vines, Sutton Valence, Maidstone.

1902 Brewerton, Elmore W., 45, Weymouth street, W.

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1867 **Bridgewater,** Thomas, LL.D. Glas., M.B. Lond., Harrow-on-the-Hill, Middlesex.

1873 Briggs, Jacob Myers, M.D., Coeymans, New York, U.S.A.

1868 Bright, George Charles, M.D., Cannes, Alpes Maritimes, France.

1902 Brincker, John Augustus Herman, M.B., B.C., Borough Hospital, Waddon, Croydon.

1857 Briscoe, John, 5, Broad street, Oxford.

1904 Briscoe, John Charlton, M.B., 48, Harley street, W.

1885 Briscoe, John F., Westbrooke House, Alton, Hants.

1903 Broadbent, J. F. H., M.D., 35, Seymour street, W.

1860 **BROADBENT,** Sir William Henry, Bart., K.C.V.O., M.D., F.R.S., 84, Brook street, W. (C. 1871-3. V.P. 1882-4.)

1886 Brockatt, Andrew Alexander, M.D., Hazeldean, Malvern.

1884 Brodie, Charles Gordon, Fernhill, Wootton Bridge, Isle of Wight.

1899 Brodie, Thomas Grigor, M.D., F.R.S. (Hon. Secretary, Section C.), 4, Lancaster terrace, Regent's Park, N.W. (C. 1900—1901. S. Com. Sect. C. 1901—.)

1871 Brown, Frederick Gordon, 17, Finsbury circus, E.C.

1903 Browne, H. S. D., 78, High street, Winchester.

1877 Bruce, J. Mitchell, M.D., 23, Harley street, W.

1902 Bruce, Samuel Noble, 15, Queensborough terrace, W.

1890 Brunton, Sir T. Lauder, M.D., D.Sc., LL.D., F.R.S., 10, Stratford place, W.

1898 Bryant, John Henry, M.D., 4, St. Thomas's street, London bridge, S.E.

1855 **BRYANT,** Thomas, M.Ch. (Trustee), 42, Norfolk square, W. (C. 1863-6. V.-P. 1877-9.)

1894 Buchanan, George Seaton, M.D., 9, Hammersmith terrace, W.

Elected

1890 BUCKLAND, FRANCIS O., M.A., M.B., C.M., Brockenhurst, Hants.

1899 BULLOCH, WILLIAM, M.D., M.B., C.M. (HON. SECRETARY, SECT. B), 66, Holland road, Kensington, W. (C. Com. Sect. B, 1901-3. S. Com. Sect. B, 1903—.)

1891 BURGHARD, FRÉDÉRIC FRANÇOIS, M.D., M.S., 86, Harley street, W.

1880 BURTON, SAMUEL HERBERT, M.B., 50, St. Giles' street, Norwich.

1900 BUSCH, JOSEPH PAUL-ZUM, M.D., Chiswell House, 133, Finsbury Pavement, E.C.

1903 BUSHNELL, FRANK GEORGE, M.D., Sussex County Hospital, Brighton.

1872 **BUTLIN**, HENRY TRENTHAM, D.C.L., 82, Harley street, W. (M.G.C. 1875-86. C. 1876-8, 1887-9. S. 1884-6. V.-P. 1891-2. P. 1895-7.)

1883 **BUXTON**, DUDLEY W., M.D., 82, Mortimer street, W.

1903 BUZZARD, EDWARD FARQUHAR, M.D., 33, Harley street, W.

1856 **BUZZARD**, THOMAS, M.D., 74, Grosvenor street, W. (C. 1869-70. V.-P. 1881-3.)

1901 CADDY, ADRIAN, M.B., 2/2, Harington street, Calcutta.

1899 CADDY, ARNOLD, 2/2, Harington street, Calcutta.

1893 CALEY, HENRY ALBERT, M.D., 24, Upper Berkeley street, W.

1897 CALVERT, JAMES, M.D., 113, Harley street, W.

1905 CAMMIDGE, PERCY JOHN, M.B., 2, Beaumont street, Portland place, W.

1892 CAMPBELL, HENRY JOHNSTONE, M.D., 36, Manningham lane, Bradford.

1905 CANDLER, JOHN PYCOCK, M.B., B.C., 65, Shepherd's Bush road, W.

1897 **Carwardine**, THOMAS, M.S., 16, Victoria square, Clifton, Bristol.

1877 CASSON, JOHN HORNSBY, H.B.M. Legation, Teheran, Persia.

1899 CAUTLEY, EDMUND, M.D., 15, Upper Brook street, W.

1864 CAY, CHARLES VIDLER, Deputy Surgeon General. Address uncommunicated.

1869 CHAFFERS, EDWARD, Abbotsrood, Milnthorpe road, Eastbourne.

1884 CHAVASSE, THOMAS FREDERICK, M.D., C.M., 22, Temple row, Birmingham.

1901 CHEATLE, G. LENTHAL, 117, Harley Street, W.

1879 CHEYNE, WILLIAM WATSON, C.B., M.B., C.M., F.R.S., 75, Harley street, W. (C. 1885-7. M.G.C. 1890-6. V.-P. 1892-3. P. 1899—1902.)

1873 CHISHOLM, EDWIN, M.D., 44, Rosslyn gardens, Darlinghurst, near Sydney, New South Wales [care of Messrs. Dawson, 121, Cannon street, E.C.].

1865 **CHURCH**, Sir WILLIAM SELBY, Bart., K.C.B., 130, Harley street, W. (M.G.C. 1869-74. C. 1871-3. V.-P. 1894-6.)

1868 **CHURCHILL**, FREDERICK, M.D., 4, Cranley gardens, Queen's gate, S.W.

1898 CHURTON, THOMAS, M.D., 35, Park square, Leeds.

1861 **CLAPTON**, EDWARD, M.D., Towercroft, 41, Eltham road, Lee, S.E.

1872 CLARK, ANDREW, 71, Harley street, W.

1886 CLARK, FRANCIS WILLIAM, M.B., Victoria, Hong Kong.

1885 CLARKE, JOHN MICHELL, M.D., 28, Pembroke road, Clifton, Bristol.

1881 CLARKE, W. BRUCE, M.B., 51, Harley street, W. (C. 1892-4.)

1904 CLELAND, JOHN BURTON, M.D., Parkside, Adelaide, South Australia.

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1899 CLEVELAND, ARTHUR JOHN, M.D., 45, Shooter's Hill road, Blackheath Park, S.E.

1875 **CLUTTON**, HENRY HUGH, M.A., 2, Portland place, W. (C. 1884-6. M.G.C. 1889-94. V.-P. 1892-3.)

1865 **Coates**, CHARLES, M.D., 10, Circus, Bath.

1892 COLE, ROBERT HENRY, M.D., Moorcroft, Hillingdon, Uxbridge.

1886 COLLIER, WILLIAM, M.D., High street, Oxford.

1888 COLLINS, Sir WILLIAM JOB, M.D., M.S., 1, Albert terrace, Regent's park, N.W.

1878 COLLYNS, R. T. POOLE, Kingsley, Lingfield road, Wimbledon, S.W.

1888 COLMAN, WALTER STACY, M.D., 9, Wimpole street, W.

1882 COLQUHOUN, DANIEL, M.D., Dunedin, New Zealand.

1905 COLWELL, HECTOR ALFRED, M.B., 55, Bridge road, Hornsey, N.

1896 CONNELL, W. T., M.D., Kingston, Canada.

1891 COOK, HERBERT G. GRAHAM, M.D., 22, Newport road, Cardiff.

1858 COOKE, R. T. E. BARRINGTON, 15, St. Nicholas cliff, Scarborough, Yorkshire.

1866 COOMBS, ROWLAND HILL, M.D., Mill street, Bedford.

1892 COOPER, C. DUDLEY [address uncommunicated].

1903 COOPER, PERCY ROBERT, M.D., B.Sc., Glenthorne, The Downs, Bowdon, Cheshire.

1900 CORNER, EDRED MOSS, M.B., 37, Harley street, W.

1899 CORNER, HARRY, M.D., Brook House, Southgate, N.

1876 COTTLE, WYNDHAM, M.D., 39, Hertford street, W.

1861 **COUPER**, JOHN, 80, Grosvenor street, W. (C. 1870-2.)

1873 **COUPLAND**, SIDNEY, M.D., 16, Queen Anne street, W. (M.G.C. 1882-6. C. 1878-81, 1889-91. S. 1886-8. V.-P. 1892-3. T. 1894—1903.)

1904 COVENTON, CHARLES ARTHUR, 111, Woodstock road, Oxford.

1897 CRAWFURD, RAYMOND H. P., M.D., 71, Harley street, W. (C. Com. Sect. A, 1902-4.)

1884 CRICHTON, GEORGE, M.D., 96, Earl's Court road, W.

1873 CRIPPS, WILLIAM HARRISON, 2, Stratford place, W. (C. 1883-5. V.-P. 1893-4.)

1877 **CROCKER**, HENRY RADCLIFFE, M.D., 121, Harley street, W. (C. 1887-9. V.-P. 1897-9.)

1886 CROOKSHANK, EDGAR, M.B., Saint Hill, East Grinstead, Sussex. (C. 1890-3. V.-P., 1900-2.)

1875 CROSS, FRANCIS RICHARDSON, 5, The Mall, Clifton, Bristol.

1889 CUFF, ROBERT, M.B., 1, The Crescent, Scarborough.

1871 CUMBERBATCH, A. ELKIN, 11, Park crescent, Portland place, W.

1893 CURTIS, HENRY JONES, M.D., Memorial Hospital, Buluwayo, S. Africa.

1884 DAKIN, W. RADFORD, M.D., B.S., 8A, Grosvenor street, Grosvenor square, W.

1883 DALTON, NORMAN, M.D., 4, Mansfield street, W. (C. Com. Sect. A, 1901-3.)

1883 DAVIS, EDWIN HARRY, West Hartlepool.

1859 **Davis**, FRANCIS WILLIAM, R.N.

Elected

1879 DAVY, HENRY, M.D., 29, Southernhay, Exeter.

1894 DAWSON, BERTRAND, M.D., 32, Wimpole street, W.

1899 DEAN, GEORGE, M.D., The Lister Institute of Preventive Medicine, Queensberry Lodge, Elstree, Herts. (C. Com. Sect. B, 1905—.)

1889 DEAN, HENRY PERCY, M.B., M.S., 69, Harley street, W. (C. 1900—1901.)

1905 DEAN, HENRY RAY, M.B., B.Ch., 53, Elm Park gardens, S.W.

1899 DE CHAZAL, EDMOND LUCIEN, M.D., Port Louis, Mauritius.

1887 DELÉPINE, SHERIDAN, M.B., C.M., The Owens College, Manchester. (C. 1899—1901.)

1880 DENT, CLINTON T., 61, Brook street, W.

1871 DICKINSON, EDWARD HARRIMAN, M.A., M.D. Address uncommunicated.

1858 **DICKINSON**, WILLIAM HOWSHIP, M.D., 10, Stanhope place, Marble arch, W. (C. 1866-8. S. 1869-71. V.-P. 1872-4. P. 1889-90.)

1900 DIXON, W. E., M.D., 28, Benson road, Forest Hill, S.E.

1872 DIVER, EBENEZER, M.D., 7, Pittville terrace, Stanshaw road, Portsmouth.

1872 DORAN, ALBAN HENRY GRIFFITHS, 9, Granville place, W. (C. 1882-4. V.-P. 1894-6.)

1893 DOWSON, WALTER, M.D., Newcome, Stanley road, Sutton, Surrey.

1877 DRAKE-BROCKMAN, EDWARD F., 14, Welbeck street, W.

1880 DRESCHFELD, JULIUS, M.D., 3, St. Peter's square, Manchester. (C. 1896-9.)

1893 DRYSDALE, JOHN HANNAH, M.D., 11, Devonshire place, W. (C. Com. Sect. A, 1904—.)

1865 **DUCKWORTH**, Sir DYCE, M.D., LL.D., 11, Grafton street, Bond street, W. (C. 1877.)

1847 **DUDGEON**, ROBERT E., M.D., 22, Carlton hill, St. John's Wood, N.W.

1902 DUDGEON, L. S., 6, Powis gardens, Bayswater, W.

1871 DUKES, CLEMENT, M.D., B.S., Sunnyside, Rugby.

1877 DUNBAR, J. J. MACWHIRTER, M.D., Hedingham House, Clapham common, S.W.

1889 DUNCAN, JOHN, M.D., St. Petersburg.

1884 DUNN, LOUIS ALBERT, M.B., M.S., 51, Devonshire street, Portland place, W.

1879 DURHAM, FREDERIC, M.B., 52, Brook street, W.

1899 EASTES, GEORGE LESLIE, M.B., B.Sc., 35, Gloucester terrace, W.

1901 EASTWOOD, A., M.D., Tuberculosis Commission, Stansted, Essex.

1893 ECCLES, WILLIAM MCADAM, M.S., 124, Harley street, W.

1892 EDDOWES, ALFRED, M.D., 28, Wimpole street, W.

1904 EDMUNDS, ARTHUR, M.S., 20, Upper Wimpole street, W.

1880 **EDMUNDS**, WALTER, M.C., 2, Devonshire place, Portland place, W. (C. 1892-4. C. Com. Sect. C, 1901-2.)

1882 EDWARDS, F. SWINFORD, 55, Harley street, W.

1889 ELAM, WILLIAM HENRY, New Barnet, Herts.

1883 ELDER, GEORGE, M.D., 17, Regent street, Nottingham.

1867 ELLIS, JAMES, M.D., Coburg street, Fratton, Portsmouth, and California.

Elected

1902 EMANUEL, JOSEPH GEORGE, M.B., B.S., B.Sc., 47, Newhall street, Birmingham.

1902 EMERY, WALTER D'ESTE, M.D., 141, Harley street, W.

1863 ENGELMANN, GEORGE JULIUS, M.D., A.M., 336, Beacon street, Boston, Mass., U.S.A.

1879 EVE, FREDERIC S., 125, Harley street, W. (M.G.C. 1884-94. C. 1885-7. V.-P. 1895-7.)

1876 EWART, JAMES COSSAR, M.B., C.M., F.R.S., School of Medicine, Edinburgh.

1881 EWART, Sir JOSEPH, M.D., Bewcastle, Dyke road, Brighton.

1877 EWART, WILLIAM, M.D., 33, Curzon street, W. (C. 1889-91.)

1859 Ewens, JOHN, 17, Redland Grove, Bristol.

1887 EYLES, CHARLES HENRY, Gold Coast Colony.

1897 EYRE, JOHN W. H., M.D., The Bacteriological Laboratory, Guy's Hospital, S.E. (C. Com. Sect. B, 1904—.)

1889 FAIRBANK, FREDERICK ROYSTON, M.D., Hillside, Westcott, Dorking.

1894 FAWCETT, JOHN, M.D., 66, Wimpole street, W. (C. Com. Sect. A, 1902-5.)

1872 FENN, EDWARD L., M.D., Nayland, Colchester.

1902 FENNELL, CHARLES HENRY, M.A., M.B., Tooting Bec Asylum, S.W.

1872 FENWICK, JOHN C. J., M.D., Long Framlington, Morpeth.

1892 FENWICK, W. SOLTAU, M.D., 29, Harley street, W.

1885 FÉRÉ, CHARLES, M.D., Médecin de Bicêtre; Boulevard St. Michel 37, Paris.

1904 FIELDING-OULD, ROBERT, M.D., B.Ch., 94, Mount street, Berkeley square, W.

1897 FISHER, THEODORE, M.D., 25, Pembroke road, Clifton, Bristol.

1893 FLETCHER, H. MORLEY, M.A., M.D., B.C., 98, Harley street, W. (C. Com. Sect. A, 1903—. S. Sect. A, 1901-3.)

1904 FORBES, JAMES GRAHAM, M.D., 10, Bentinck street, Cavendish square, W.

1866 Foster, Sir BALTHAZAR WALTER, M.D., M.P., 30, Grosvenor road, Westminster.

1891 FOULERTON, ALEXANDER GRANT RUSSELL, Rhynie, Hayward's Heath, Sussex. (C. 1900—1901. C. Com. Sect. B, 1903—. S. Sect. B, 1901-3.)

1880 FOWLER, JAMES KINGSTON, M.A., M.D., 35, Clarges street, W. (C. 1887-8.)

1878 FOX, THOMAS COLCOTT, B.A., M.B., 14, Harley street, W. (C. 1892-4.)

1902 FREMLIN, H. STUART, Government Lymph Laboratory, Chelsea Bridge, S.W.

1896 FREYBERGER, LUDWIG, M.D., 41, Regent's park road, N.W. (C. Com. Sect. A, 1902-3.)

1891 FRIPP, Sir ALFRED DOWNING, C.B., M.V.O., M.S., 19, Portland place, W.

1864 FRODSHAM, JOHN MILL, M.D., Streatham, S.W.

1899 FÜRTH, KARL, M.D., 39, Harley street, W.

1894 FURNIVALL, PERCY, 28, Weymouth street, Portland place, W.

Elected

1893 FYFFE, WILLIAM KINGTON, M.B., 1, Boullcott street, Wellington, New Zealand.

1880 GABBETT, HENRY SINGER, M.D., 8, Chiswick place, Eastbourne.

1858 **Gairdner**, Sir WILLIAM TENNANT, K.C.B., M.D., LL.D.Edin., F.R.S., 32, George square, Edinburgh. (V.-P. 1891-2.)

1890 GALLOWAY, JAMES, M.A., M.D., 54, Harley street, W. (C. 1899-1902. Com. Sect. A, 1901-2.)

1870 GALTON, JOHN H., M.D., Sylvan road, Upper Norwood, S.E.

1846 **GARROD**, Sir ALFRED BARING, M.D., F.R.S., 10, Harley street, W. (C. 1851. V.-P. 1863-5.)

1892 GARROD, ARCHIBALD EDWARD, M.D. (HON. SECRETARY, SECT. D), 9, Chandos street, Cavendish square, W. (C. 1898—1901. S. Sect. D, 1901—.)

1879 GARSTANG, THOMAS WALTER HARROPP, Englefield, Delamer road, Bowdon, Cheshire.

1872 GARTON, WILLIAM, M.D., Inglewood, Aughton, near Ormskirk, Lancashire.

1902 GASK, G. E., M.B., 45, Weymouth street, W.

1880 GIBBES, HENRAGE, M.B., University of Michigan, Ann Arbor, Michigan, U.S.A.

1853 **GIBBON**, SEPTIMUS, M.D., 39, Oxford terrace, Hyde park, W.

1878 GIBBONS, ROBERT A., M.D., 29, Cadogan place, S.W.

1876 GILL, JOHN, M.D., 30, West mall, Clifton, Bristol.

1881 GLYNN, THOMAS ROBINSON, M.D., 62, Rodney street, Liverpool.

1898 GOADBY, KENNETH WELDON, 21, New Cavendish street, Portland place, W. (C. Com. Sect. B, 1905—.)

1873 GODLEE, RICKMAN JOHN, M.B., M.S., 19, Wimpole street, W. (M.G.C. 1875-84. C. 1877-80, 1891-2. S. 1887-9. V.-P. 1893-4, 1902-5. Chairman, Sect. A.)

1878 **GOLDING-BIRD**, CUTHBERT H., M.B., B.S., 12, Queen Anne street, W. (C. 1885-7. V.-P. 1894-6.)

1902 GOODBODY, FRANCIS WOODCOCK, M.D., 6, Chandos street, W.

1871 GOODHART, JAMES FREDERIC, M.D., 25, Portland place, W. (M.G.C. 1874-86. C. 1876-8, 1886-8. S. 1883-5. V.-P. 1892-3.)

1894 GOSSAGE, ALFRED MILNE, M.B., B.Ch., 54, Upper Berkeley street, W.

1875 GOULD, ALFRED PEARCE, M.S., 10, Queen Anne street, W. (C. 1883-5. V.-P. 1898-1900.)

1870 GOWERS, Sir WILLIAM, M.D., F.R.S., 50, Queen Anne street, W. (C. 1878-9. V.P. 1896-7.)

1888 GRANT, J. DUNDAS, M.A., M.D., C.M., 18, Cavendish square, W.

1900 GREEN, ALAN B., M.A., M.D., B.C., 31, Cheyne court, Chelsea, S.W.

1895 GREEN, CHARLES DAVID, M.D., The Ferns, South street, Romford. (C. 1900-2. C. Com. Sect. A, 1901-2.)

1867 GREEN, T. HENRY, M.D., 74, Wimpole street, W. (M.G.C. 1869-83. C. 1871-3, 1878-9. S. 1875-6. V.-P. 1886-8.)

1873 GREENFIELD, WILLIAM SMITH, M.D., B.S., 7, Heriot row, Edinburgh. (M.G.C. 1874-81. C. 1877-80. V.-P. 1893-4.)

1886 GREVES, EDWIN HYLA, M.D., Rodney House, Suffolk road, Bournemouth.

Elected

1887 GRIFFITHS, JOSEPH, M.D., C.M., 63, Trumpington street, Cambridge.
1876 GRIFFITHS, THOMAS D., M.D., Hearne Lodge, Swansea.
1900 GRUBE, KARL, M.D., Neuenahr, Germany.
1899 GRUBER, R., M.D., 67, Wimpole street, W.
1905 GRÜNBAUM, ALBERT SIDNEY FRANKAU, M.D., The Drive, Roundhay, Leeds.
1902 GRÜNBAUM, O. F. F., M.D., D.Sc., 30A, Wimpole street, W.

1887 HABERSHON, SAMUEL HERBERT, M.D., 88, Harley street, W. (C. Com. Sect. A, 1902-4.)
1851 **HACON**, E. DENNIS, 269, Mare street, Hackney, N.E. (C. 1872.)
1892 HADLEY, WILFRED JAMES, M.D., 33, Queen Anne street, W.
1882 HAIG, ALEXANDER, M.D., 7, Brook street, W.
1899 HALL, ARTHUR J., M.B., 342, Glossop road, Sheffield.
1904 HALL, ISAAC WALTER, M.D., The Owens College, Manchester.
1901 HALLIBURTON, WILLIAM DOBINSON, M.D., F.R.S., Church Cottage, 17, Marylebone road, W. (V.-P., Chairman Sect. D., 1901-5.)
1894 HALLIDIE, ANDREW HALLIDIE SMITH, M.B., 50, Noord street, Johannesburg.
1886 HAMILTON, DAVID JAMES, M.B., 41, Queen's road, Aberdeen.
1890 HANDFIELD-JONES, MONTAGU, M.D., 35, Cavendish square, W.
1886 HANDFORD, HENRY, M.D., 6, Regent street, Nottingham.
1902 HANDLEY, WILLIAM SAMPSON, M.S., M.D., 51, Devonshire street, W.
1891 HANKIN, E. H., Agra, India.
1882 HARBINSON, ALEXANDER, M.D., County Lunatic Asylum, Lancaster.
1893 **HARLEY**, VAUGHAN, M.D., 25, Harley street, W. (C. Com. Sect. D, 1901—.)
1901 HARMER, W. D., The Warden's House, St. Bartholomew's Hospital, E.C.
1879 HARRIS, VINCENT DORMER, M.D., Woodrouffe House, Milford-on-Sea, near Lymington, Hants.
1896 HARTLEY, PERCIVAL HORTON-SMITH, M.D., B.C., 19, Devonshire street, W.
1891 HASLAM, WILLIAM F., 54, Newhall street, Birmingham.
1904 HAWES, COLIN SADLER, Albany General Hospital, Grahamstown, South Africa.
1899 HAWKES, CLAUDE SOMERVILLE, Glencairn, Wickham terrace, Brisbane, Queensland, Australia.
1886 HAWKINS, FRANCIS HENRY, M.D., 73, London street, Reading.
1890 HAWKINS, HERBERT PENNELL, M.D., 56, Portland place, W. (C. 1898—1901.)
1900 HEATON, CHARLES, Westgate-on-Sea, Thanet, Kent.
1892 HEATON, GEORGE, M.B., B.Ch., 47, Newhall street, Birmingham.
1881 HEBB, RICHARD G., M.A., M.D., 50, Ridgmount gardens, Gower street, W.C. (M.G.C. 1891—1900. C. 1891-3. 1898—1901. S. 1896-7.)
1884 HEBBERT, CHARLES ALFRED, care of C. Baylor, 7, Water street, Boston, U.S.A.
1901 HÉDIN, SVEN GUSTAV, M.D., Lister Institute of Preventive Medicine, Chelsea bridge, S.W. (C. Com. Sect. D, 1901-4.)

Elected

1879 HENDERSON, GEORGE COURTENAY, M.D., Kingston, Jamaica, West Indies.

1869 HENSLEY, PHILIP J., M.D., 4, Henrietta street, W.

1884 HERRINGHAM, WILMOT PARKER, M.D., 40, Wimpole street, W. (C. 1894-7.)

1892 HEWLETT, RICHARD TANNER, M.D., Bacteriological Laboratory, King's College, Strand, W.C. (C. Com. Sect. B, 1902—.)

1897 HICHENS, PEVERELL S., M.B., B.Ch., 45, Sheep street, Northampton.

1900 HILLIER, WILLIAM THOMAS, Rougemont, Beaconsfield road, St. Albans.

1903 HOBDAY, F., F.R.C.V.S., 10, Silver street, Kensington, W.

1880 HOBSON, JOHN MORRISON, M.D., Glendalough, Morland road, Croydon.

1854 **HOLMES**, TIMOTHY, 6, Sussex place, Hyde park, W. (C. 1862–3. S. 1864-7. C. 1868. V.-P. 1869-71.)

1878 HOOD, DONALD WILLIAM CHARLES, C.V.O., M.D., 43, Green street, Park lane, W.

1864 HOOD, WHARTON P., M.D., 11, Seymour street, W.

1903 HOPEWELL-SMITH, ARTHUR, 26, Berkeley square, Mayfair, W.

1895 HOPKINS, FREDERICK GOWLAND, M.B., New Museums, Cambridge. (C. 1899—1905. Com. Sect. D, 1901-5. V.P., Chairman Sect. D, 1905—.)

1900 HORDER, THOMAS J., M.D., B.Sc., 141, Harley street, W.

1897 HORNE, W. JOBSON, M.B., 27, New Cavendish street, Portland place, W.

1883 HORSLEY, Sir VICTOR, M.B., B.S., F.R.S., 25, Cavendish square, W. (C. 1888-9. V.-P. 1900-1902.)

1880 **HOVELL**, T. MARK, 105, Harley street, W.

1893 HOWARD, ROBERT JARED BLISS, M.D., 31, Queen Anne street, W.

1856 **HUDSON**, JOHN, M.D., 11, Cork street, W.

1874 HUMPHREYS, HENRY, M.D., St. Mary Church road, Torquay.

1897 HUNT, E. L., c/o King, King, and Co., Bombay.

1897 HUNT, GEORGE B., M.D., 47, Albemarle crescent, Scarborough.

1888 HUNTER, WILLIAM, M.D., 103, Harley street, W. (C. 1897-1900.)

1852 **HUTCHINSON**, JONATHAN, F.R.S., 15, Cavendish square, W. (C. 1856-9. V.-P. 1872-3, 1881-3. P. 1879-80.)

1901 HUTCHISON, ROBERT, M.D., 22, Queen Anne street, W. (C. Com. Sect. D, 1905—.)

1884 HUTTON, HENRY RICHMOND, M.B., 8A, St. John street, Manchester.

1880 INGRAM, ERNEST FORTESCUE, Newcastle, Natal, S. Africa.

1886 JACKSON, ARTHUR MOLYNEUX, M.D., Kent County Asylum, Barming Heath, Maidstone.

1865 JACKSON, J. HUGHLINGS, M.D., F.R.S., 3, Manchester square, W. (C. 1872-3. V.-P. 1888-9.)

1875 JALLAND, WILLIAM HAMERTON, St. Leonard's House, Museum street, York.

1897 JAMES, GEORGE T. B., Carlisle mansions, Victoria street, S.W.

1888 JAMES, JAMES THOMAS, M.D., 30, Harley street, W.

1853 **Jardine**, JOHN LEE, The Avenue, Kew gardens, S.W.

1904 JENNINGS, JOHN FREDERICK, M.B., B.S., St. Bartholomew's Hospital, E.C.

Elected

1881 JENNINGS, WILLIAM OSCAR, M.D., 74, Avenue Marceau, Paris.

1878 JOHNSON, ARTHUR JUKES, Yorkville, Ontario, Canada.

1876 JOHNSON, CHARLES HENRY, Winton House, Basingstoke, Hants.

1901 JOHNSON, EDWARD ANGAS, M.B., B.S., St. Catharine's, Prospect, South Australia.

1888 JOHNSON, RAYMOND, M.B., B.S., 11, Wimpole street, Cavendish square, W. (C. 1896-9.)

1899 JONAS, HERBERT C., M.D., Bear street, Barnstaple.

1853 **JONES**, SYDNEY, M.B., 8A, New Cavendish street, W. (C. 1864-6. V.-P. 1886-7.)

1888 JONES, TALFOURD, M.B., St. Davids, 11, Park road, Southborough.

1862 **JONES**, THOMAS RIDGE, M.D., 4, Chesham place, S.W. (C. 1882-4.)

1898 KEEP, ARTHUR CORRIE, M.D., M.C., 14, Gloucester place, W.

1897 KELLY, CHARLES E. M., M.D., Witney, Oxon.

1901 KELYNACK, T. N., M.D., 120, Harley street, W.

1859 KIALLMARK, HENRY WALTER, 5, Pembridge gardens, W. (C. 1875-6.)

1882 KIDD, PERCY, M.D., 60, Brook street, W. (C. 1889-91.)

1852 **KINGDON**, J. ABERNETHY, 6A, Princes street, Bank, E.C.

1901 KLEIN, EDWARD EMANUEL, M.D., F.R.S., Harewood, Riverdale gardens, Twickenham Park, Twickenham. (V.-P., Chairman, Sect. B, 1901-5.)

1902 KOENIG, RENÉ PAUL, M.D., 3, Rue de la Monnaie, Geneva, Switzerland.

1903 LAKIN, CHARLES ERNEST, M.B., Middlesex Hospital, W.

1878 LANCEREAUX, ETIENNE, M.D., 44, Rue de la Bienfaisance, Paris.

1882 LANE, WILLIAM ARBUTHNOT, M.B., M.S., 21, Cavendish square, W. (C. 1891-3.)

1904 LANGMEAD, FREDERICK, M.B., Hospital for Sick Children, Great Ormond street, W.C.

1869 LARCHER, O., M.D.Par., 97, Rue de Passy, Paris. [M. Kliensieck, Libraire, Rue de Lille 11, Paris, per Messrs. Longmans.]

1884 LARDER, HERBERT, Whitechapel Infirmary, Vallance road, N.E.

1897 LATHAM, ARTHUR C., M.D., 44, Brook street, W.

1873 LATHAM, PETER WALLWORK, M.D., 17, Trumpington street, Cambridge.

1853 LAWRENCE, HENRY JOHN HUGHES, Picton House, Llandowror, St. Clears. (C. 1873-5.)

1892 LAWRENCE, THOMAS WILLIAM PELHAM, M.B., 12, North hill, Highgate, N. (C. Com. Sect. A, 1901-3.)

1893 LAWSON, ARNOLD, M.D., 12, Harley street, W.

1879 LAYCOCK, GEORGE LOCKWOOD, M.B., Melbourne, Victoria, Australia.

1891 LAZARUS-BARLOW, WALTER SYDNEY, M.D., Fernholme, Woodside Park, N. Finchley, N. (C. Com. Sect. C, 1901-4.)

1904 LEATHEM, ALFRED NEWMAN, Gwydor Cottage, Elmer's end, Beckenham.

1901 LEATHES, JOHN BERESFORD, M.B., 9, Albert Bridge road, Battersea park, S.W. (C. Com. Sect. D, 1904—.)

1875 LEDIARD, HENRY AMBROSE, M.D., 35, Lowther street, Carlisle. (C. 1897-1900.)

1877 **LEES**, DAVID B., M.D., 22, Weymouth street, W. (C. 1890-2.)

Elected

1867 LEES, JOSEPH, M.D., 21, Brixton road, S.W.

1877 LEESON, JOHN RUDD, M.D., C.M., 6, Clifden road, Twickenham.

1868 LEGG, JOHN WICKHAM, M.D. (Travelling.) (C. 1874-5.)

1902 LEGG, THOMAS PERCY, M.B., 141, Harley street, W.

1892 LEITH, ROBERT FRASER CALDIE, M.B., C.M., B.Sc.

1892 **Leudet**, ROBERT, 72, Rue de Bellechasse, Paris, France.

1897 LISTER, THOMAS DAVID, 50, Brook street, W.

1895 LITTLE, ERNEST GRAHAM GORDON, M.D., 61, Wimpole street, W.

1889 LITTLE, JOHN FLETCHER, M.B., 32, Harley street, W.

1862 **LITTLE**, LOUIS S., 31, Grosvenor street, W.

1896 LITTLEWOOD, HARRY, 25, Park square, Leeds.

1874 LIVEING, EDWARD, M.D., 52, Queen Anne street, W.

1863 **LIVEING**, ROBERT, M.D., 11, Manchester square, W. (C. 1876.)

1881 LUBBOCK, MONTAGU, M.D., 19, Grosvenor street, W.

1897 LUCAS, ALBERT, 9, Easy row, Birmingham.

1873 LUCAS, R. CLEMENT, M.B., B.S., 50, Wimpole street, W. (C. 1883-5.)

1879 LUNN, JOHN REUBEN, St. Marylebone Infirmary; Rackham street, Ladbroke grove road, W. (C. 1897-1900.)

1887 LYON, THOMAS GLOVER, M.D., 1, Victoria square, S.W.

1904 MCDONALD, STUART, *c/o* Fairbairn, 40, Warrender park road, Edinburgh.

1893 MCFADYEAN, JOHN, M.B., Royal Veterinary College, Great College street, N.W. (C. 1899—. Com. Sect. B, 1901-4.)

1896 MACFADYEN, ALLAN, M.D., B.Sc., Lister Institute of Preventive Medicine, Chelsea gardens, S.W. (C. 1900-3. Com. Sect. B, 1901-3.)

1899 MCGAVIN, LAWRIE H., 6, Mansfield street, Cavendish square, W.

1885 MACKENZIE, HECTOR WILLIAM GAVIN, M.A., M.D., 34, Upper Brook street, Grosvenor square, W. (C. 1895-7.)

1870 MACKENZIE, JOHN T., Bombay, India.

1878 MACKENZIE, SIR STEPHEN, M.D., Merrycourt, Great Bookham, Leatherhead, Surrey. (C. 1888-90.)

1902 MACKIE, FREDERIC PERCIVAL, Agents, *c/o* Grindlay, Groom and Co., Bombay.

1865 MACLAURIN, HENRY NORMAND, M.D., 187, Macquarie street, Sydney, New South Wales.

1896 MCWEENEY, EDMOND JOSEPH, M.D., M.Ch., 84, St. Stephen's green, Dublin.

1885 MAGUIRE, ROBERT, M.D., 4, Seymour street, W.

1877 **MAKINS**, GEORGE HENRY, C.B., 47, Charles street, Berkeley square, W (C. 1889-91. V.-P. 1899-1901.)

1887 MALCOLM, JOHN DAVID, M.B., C.M., 13, Portman street, W.

1892 MANN, HAROLD EDWARD, Alderney.

1890 MANSON, Sir PATRICK, K.C.M.G., M.D., C.M., F.R.S., 21, Queen Anne street, W. (C. 1900-1.)

1876 MAPLES, REGINALD, Kingsclere, near Newbury.

1904 MARRIAGE, HERBERT JAMES, M.B., B.S., 109, Harley street, W.

1868 MARSH, F. HOWARD, M.C., 14, Hertford street, Mayfair, W. (C. 1876-7.) (V.-P 1889-90.)

Elected

1904 MARTIN, CHARLES J., M.B., D.Sc., F.R.S., Lister Institute of Preventive Medicine, Chelsea gardens, S.W. (C. Com. Sect. C, 1904—.)

1904 MARTIN, ERNEST WILLIAM, M.B., Ch.B., 3, Hamlet road, Upper Norwood, S.E.

1887 MARTIN, SIDNEY, M.D., B.S., F.R.S., 10, Mansfield street, W. (C. 1893-6. V.-P. 1900-1902.)

1889 MASON, DAVID JAMES, M.D., Rosemont, Maidenhead.

1898 MASTERMAN, ERNEST WILLIAM GURNEY, Surgeon, English Mission Hospital, Jerusalem, Syria.

1892 MASTERS, JOHN ALFRED, M.D., 94, Knightsbridge, S.W.

1884 MAUDSLEY, HENRY CARR, M.D., 11, Spring street, Melbourne, Victoria.

1902 MAVROGORDATO, ANTHONY, 8, Ladbroke gardens, W.

1897 MAXWELL, J. P., c/o E.P. Mission, Eng Chhun, Amoy, China.

1900 MAXWELL, JAMES LAIDLAW, M.D., E.P. Mission, Yai-nan-fu, Formosa *vid* Hong Kong.

1852 **MAY**, GEORGE, M.B., Reading.

1888 MAY, WILLIAM PAGE, M.D., B.Sc., 9, Manchester square, W., and Helouan, near Cairo, Egypt (November to April).

1881 MAYLARD, ALFRED ERNEST, M.B., 4, Berkeley terrace, Glasgow.

1874 MEREDITH, WILLIAM APPLETON, C.M., 21, Manchester square, W.

1894 MICHELS, ERNST, M.D., 48, Finsbury square, E.C.

1900 MILBURN, LESLIE, 3, Cyprus street, Wakefield, Yorks.

1901 MOORE, ALFRED, Reculver Villa, Cheam road, Sutton, Surrey.

1899 MOORE, FREDERICK CRAVEN, M.D., The Priory, Ardwick Green, Manchester.

1879 MOORE, NORMAN, M.D., 94, Gloucester place, Portman square, W. (C. 1885-7. M.G.C. 1889-1900. V.-P. 1895-7.)

1875 MORGAN, JOHN H., C.V.O., 68, Grosvenor street, W. (C. 1886-8.)

1874 MORISON, ALEXANDER, M.D., C.M., 14, Upper Berkeley street, W.

1869 **MORRIS**, HENRY, M.A., M.B. (TRUSTEE), 8, Cavendish square, W. (C. 1877-9, 1884-6. S. 1881-3. V.-P. 1888-9.)

1879 MORRIS, MALCOLM ALEXANDER, 8, Harley street, W.

1894 MORRICE, GEORGE GAVIN, M.D., Holy Trinity Vicarage, Weymouth.

1891 MORTON, CHARLES A., 14, Vyvyan terrace, Clifton, Bristol.

1875 MORTON, JOHN, M.B., Guildford.

1884 MOTT, FREDERICK WALKER, M.D., F.R.S., 25, Nottingham place, W. (C. 1891-3. V.-P. 1899-1901.)

1900 MUIR, ROBERT, M.D., 4, Alfred terrace, Glasgow.

1893 MUMMERY, JOHN HOWARD, 10, Cavendish place, W.

1899 MURRAY, GEORGE R., M.D., 11, Ellison place, Newcastle-on-Tyne.

1885 MURRAY, HUBERT MONTAGUE, M.D., 25, Manchester square, W. (C. 1896-9.)

1894 MURRAY, JOHN, M.B., B.Ch., 110, Harley street, W.

1901 NABARRO, DAVID, M.D., B.Sc., D.P.H., 4, Albemarle mansions, Heath Drive, N.W.

1887 NASON, EDWARD NOEL, M.D., 80, Abbey street, Nuneaton.

1904 NEAVE, SHEFFIELD, Mill Green park, Ingatestone, Essex.

1875 NEWBY, CHARLES HENRY, St. Mary's Broad, Park avenue, Ilfracombe.

Elected

1902 Newland, Thomas Simpson, M.B., Ch.B., North terrace, Adelaide S. Australia.
1865 Newman, William, M.D., Stamford, Lincolnshire.
1895 Nias, J. Baldwin, M.D., 5, Rosary gardens, S. Kensington, S.W.
1868 Nicholls, James, M.D., Trekenning House, St. Columb, Cornwall.
1876 Nicholson, Frank, M.D., 29, Albion street, Hull.
1864 **NORTON**, Arthur T., C.B., Leyfields Wood, Ashampstead, Berks. (C. 1877-9.)
1883 Norvill, Frederic Harvey, M.B., Dibrooghur, India.

1880 O'Connor, Bernard, M.D., 32, Old Buildings, Lincoln's Inn, W.C.
1873 O'Farrell, Sir George Plunkett, M.D., 19, Fitzwilliam square, Dublin.
1894 Ogle, Cyril, M.B., 96, Gloucester place, W. (C. 1899-1901.)
1888 Openshaw, Thomas Horrocks, C.M.G., M.S., 16, Wimpole street, W.
1892 Ord, William Wallis, M.D., The Hall, Salisbury.
1879 Ormerod, Joseph A., M.D., 25, Upper Wimpole street, W. (C. 1887-9.)
1875 **OSBORN**, Samuel, Maisonnette, Datchet, Bucks.
1865 Owles, James Allden, M.D., Hill View, Woking, Surrey.

1884 Paget, Stephen, 70, Harley street, W. (C. 1894-7.)
1895 Pakes, Walter Charles, Government Laboratory, Pretoria, South Africa. (C. Com. Sect. B, 1901-2.)
1897 Parfitt, Charles D., M.D., London, Canada.
1898 Parker, Arthur Percy, M.B., B.Ch., 27, Beaumont street, Oxford.
1874 Parker, Rushton, M.B., B.S., 59, Rodney street, Liverpool.
1853 **PARKINSON**, George, Orchard Dene, Henley-on-Thames.
1901 Parsons, John Herbert, M.B., B.S., B.Sc., 27, Wimpole street, W.C.
1882 Pasteur, William, M.D., 4, Chandos street, W. (C. 1893-6.)
1885 Paul, Frank Thomas, 38, Rodney street, Liverpool.
1865 **PAVY**, Frederick William, M.D., LL.D., F.R.S., 35, Grosvenor street, W. (C. 1872-4. V.-P. 1891-2. V.-P., Chairman Sect. C, 1901—. P. 1893-4.)
1868 Payne, Joseph Frank, M.D. (Trustee), 78, Wimpole street, W. (M.G.C. 1872-85. C. 1873-5, 1883-5. S. 1880-2. V.-P. 1888-9. V.-P., Chairman Sect. A, 1901-2. P. 1897-8.)
1872 Pearce, Joseph Chaning, M.D., C.M., Montague House, St. Lawrence-on-Sea, Kent.
1879 Peel, Robert, 130, Collins street East, Melbourne, Victoria.
1899 Pembrey, Marcus Seymour, M.D., B.Ch., Guy's Hospital, S.E. (C. Com. Sect. C, 1904—.)
1889 Penberthy, John, Royal Veterinary College, Camden Town, N.W.
1887 Penrose, Francis George, M.D., 84, Wimpole street, W.
1884 Pepper, Augustus Joseph, M.B., C.M., 13, Wimpole street, W.
1900 Perkins, Joseph John, M.B., 41, Wimpole street, Cavendish square, W.
1899 Pernet, George, 152, Harley street, W.
1888 Perry, Sir Edwin Cooper, M.D., Superintendent's House, Guy's Hospital, S.E.
1904 Petrie, George Ford, M.D., 66, Holland Road, Kensington, W.

Elected

1902 PHEAR, ARTHUR G., M.D., 47, Weymouth street, W.

1878 PHILIPPS, SUTHERLAND REES, M.D., St. Ann's heath, Virginia Water Chertsey.

1878 PHILLIPS, JOHN WALTER, 30, Stanley street West, Melbourne, Victoria.

1893 PINKERTON, ROBERT A., M.A., M.D., 15, South Norwood hill, S.E.

1884 PITT, GEORGE NEWTON, M.D., 15, Portland place, W. (M.G.C. 1889 97. C. 1890-2, 1896-9. S. 1894-6. V.-P. 1899-1901.)

1876 PITTS, BERNARD, M.A., M.C., 109, Harley street, W. (C. 1888-90.)

1899 PLIMMER, HENRY GEORGE, 3, Hall road, N.W. (C. Com. Sect. B, 1901-3.)

1883 POLAND, JOHN, 2, Mansfield street, Cavendish square, W.

1882 POLLARD, BILTON, M.B., B.S., 24, Harley street, W. (C. 1895-7.)

1850 POLLOCK, JAMES EDWARD, M.D., 37, Collingham place, W. (C. 1862-4. V.-P. 1879-81.)

1879 **POTTER**, HENRY PERCY, M.D., St. Mary Abbotts Infirmary, Marloes road, Kensington, W.

1866 POWELL, Sir RICHARD DOUGLAS, Bart., K.C.V.O., M.D., P.R.C.P., 62, Wimpole street, W. (C. 1873-5, 1881-3. S. 1877-9. V.-P. 1887-8.)

1884 **POWER**, D'ARCY, M.A., M.B., 10A, Chandos street, W. (C. 1891-3. 1899-1902. Com. Sect. A, 1901-2. M.G.C. 1897-1900. S. 1897-9.)

1865 POWER, HENRY, Bagdale Hall, Whitby. (C. 1876-7.)

1900 POYNTON, FREDERICK JOHN, M.D., 19, Portman street, W. (C. Com. Sect. A, 1905—.)

1887 PRATT, WILLIAM SUTTON, M.D., Penrhos House, Rugby.

1902 PRICE, F. W., M.B., 77, Wimpole street, W.

1884 PRICE, JOHN A. P., M.D., 124, Castle street, Reading.

1900 PRICE-JONES, CECIL, M.B., 7, Claremont road, Surbiton, Surrey.

1888 PRIMROSE, ALEXANDER, M.B., C.M., 100, College street, Toronto, Canada.

1895 PURVIS, WILLIAM PRIOR, M.D., 2, Avenue place, Southampton.

1865 PYE-SMITH, PHILIP HENRY, M.D., F.R.S. (TREASURER), 48, Brook street, W. (C. 1874-7. V.-P. 1890-1. Chairman Sect. A, 1905—. T. 1903—.)

1897 RANKIN, GUTHRIE, M.D., 4, Chesham street, S.W.

1890 **Ransom**, WILLIAM BRAMWELL, M.D., The Pavement, Nottingham.

1891 RATCLIFFE, JOSEPH RILEY, M.B., C.M., Wake green, Moseley.

1887 RAVEN, THOMAS FRANCIS, Broadstairs, Kent.

1870 RAY, EDWARD REYNOLDS, 15A, Upper Brook street, W.

1875 REID, ROBERT WILLIAM, M.D., C.M., 8, Queen's gardens, Aberdeen,

1901 REID, ST. GEORGE CAULFIELD, Brigstock House, Thornton Heath, Surrey.

1901 REISSMANN, CHARLES, M.B., St. Peter's, College Town, Adelaide, S. Australia.

1881 RENNER, WILLIAM, Wilberforce street, Free Town, Sierra Leone.

1893 RENNIE, GEORGE EDWARD, M.D., College street, Hyde park, Sydney, N.S.W.

1895 RITCHIE, JAMES, M.D., 28, Beaumont street, Oxford. (C. Com. Sect. B, 1903-5.)

1901 RIVIERE, CLIVE, M.D., 19, Devonshire street, W.

1865 **Roberts**, DAVID LLOYD, M.D., 11, St. John's street, Manchester.

Elected

1871 ROBERTS, FREDERICK THOMAS, M.D., 102, Harley street, W. (C. 1883-5.)

1878 ROBERTS, WILLIAM HOWLAND, M.D., Surgeon, Madras Army.

1888 ROBERTSON, ROBERT, M.D., The Bungalow, Ventnor, Isle of Wight.

1885 ROBINSON, ARTHUR HENRY, M.D., St. Mary's Infirmary, Highgate hill, N.

1882 ROBINSON, TOM, M.D., 9, Princes street, Cavendish square, W.

1904 ROBSON, A. W. MAYO, 8, Park crescent, Portland place, W.

1888 ROLLESTON, HUMPHRY DAVY, M.A., M.D. 55, Upper Brook street, Grosvenor square, W. (C. 1894-7. 1900-1902. Com. Sect. A, 1901-2. M.G.C. 1895-1900. S. 1898-1900.)

1904 ROSE, FRANK ATCHERLEY, M.B., 42, Devonshire street, Portland place, W.

1858 ROSE, HENRY COOPER, M.D., 16, Warwick road, Maida hill, N.W. (C. 1873-4.)

1875 ROSSITER, GEORGE FREDERICK, M.B., Cairo Lodge, Weston-super-Mare.

1877 ROTH, BERNARD, 38, Harley street, W., and "Wayside," 1, Preston park avenue, Brighton.

1888 ROUGHTON, EDMUND WILKINSON, M.D., 38, Queen Anne street, W.

1891 ROUILLARD, LAURENT ANTOINE JOHN, M.B., Durban, Natal.

1901 ROWLAND, SYDNEY, M.A., Lister Institute of Preventive Medicine, S.W.

1899 ROWLANDS, ROBERT P., 6, St. Thomas's street, London Bridge, S.E.

1891 RÜFFER, MARC ARMAND, M.D., The Quarantine Board, Alexandria.

1897 RUNDLE, HENRY, 13, Clarance parade, Southsea.

1900 RUSSELL, A. E., M.D., 9, Wimpole street, Cavendish square, W.

1895 RUSSELL, JAMES SAMUEL RISIEN, M.D., 44, Wimpole street, Cavendish square, W.

1891 RUSSELL, WILLIAM, M.D., 3, Walker street, Edinburgh.

1903 SALAMAN, RADCLIFFE N., M.B., Frognal End, Frognal gardens, Hampstead, N.W.

1854 SANDERSON, Sir JOHN BURDON, Bart., M.D., D.C.L., F.R.S. (PRESIDENT), 64, Banbury road, Oxford. (P. 1902—. M.G.C. 1869-76. C. 1864-7. V.-P. 1873-4.)

1902 SARGENT, PERCY WILLIAM GEORGE, M.B., B.C., St. Thomas's Hospital, S.E.

1886 SAUNDBY, ROBERT, M.D., 140B, Great Charles street, Birmingham.

1871 SAUNDERS, CHARLES EDWARD, M.D., Sussex County Lunatic Asylum, Hayward's Heath.

1901 SAUNDERS, E. A., M.B., 49, Harley street, W.

1890 SAUNDERS, FREDERICK WILLIAM, M.B., B.C., Chieveley House, Newbury.

1873 SAVAGE, GEORGE HENRY, M.D., 3, Henrietta street, Cavendish square, W. (C. 1881-3.)

1882 SAVILL, THOMAS DIXON, M.D., 60, Upper Berkeley street, W.

1902 SCHÖLBERG, H. A., M.B., University College of South Wales and Monmouthshire, Cardiff.

1891 SCHORSTEIN, GUSTAVE ISIDORE, M.B., B.Ch., 11, Portland place, W.

1901 SCOTT, Hon. G. H., M.B., B.C., Mertoun House, St. Boswells, N.B.

1902 SCOTT, S. G., M.A., M.B., Yorkshire College, Department of Medicine, Thoresby place, Leeds.

Elected

1899 SELIGMANN, CHARLES G., M.B., 15, York terrace, Regent's Park, N.W. (C. Com. Sect. A, 1905—.)

1903 SELOUS, C. F., M.B., St. Thomas's Hospital, Albert Embankment, S.E.

1877 SEMON, Sir FELIX, C.V.O., M.D., 39, Wimpole street, W. (C. 1885-7.)

1894 SEQUEIRA, JAMES HARRY, M.D., 63, Harley street, Cavendish square, W.

1872 SERGEANT, EDWARD, D.P.H., Lancashire County Council, Public Health Department, County Offices, Preston.

1876 SHARKEY, SEYMOUR J., M.D., 22, Harley street, W. (M.G.C. 1884-1895. C. 1884-6. V.-P. 1895-7.)

1880 SHATTOCK, SAMUEL G. (HON. GENERAL SECRETARY), 4, Crescent road, The Downs, Wimbledon, S.W. (M.G.C. 1884-1900. C. 1885-7. 1893-6. S. 1890-2, 1902—. V.-P. 1896-8. E. 1900—.)

1898 SHAW, HAROLD BATTY, M.D., 7, Devonshire street, W. (C. Com. Sect. A, 1903—.)

1885 SHAW, LAURISTON ELGIE, M.D., 64, Harley street, W.

1886 **SHERRINGTON**, CHARLES SCOTT, M.D., F.R.S., University College, Liverpool. (C. 1894-7.)

1856 **SHILLITOE**, BUXTON, 2, Frederick's place, E.C.

1875 SIDDALL, JOSEPH BOWER, M.D., C.M., Conybeare, Northam, Bideford.

1901 SINGER, HAROLD DOUGLAS, M.D., McCagne Buildings, Omaha, Neb., U.S.A.

1892 SLATER, CHARLES, M.B., St. George's Hospital, S.W.

1887 SMALLPEICE, WILLIAM DONALD, 10, Chester square, S.W.

1879 SMITH, E. NOBLE, 24, Queen Anne street, W.

1887 **SMITH**, FREDERICK JOHN, M.D., 138, Harley street, W.

1894 SMITH, GUY BELLINGHAM, M.B., B.S., 24, St. Thomas's street, S.E.

1900 SMITH, J. LORRAIN, M.D., The Medical School, Leeds. (C. Com. Sect. C, 1905—.)

1873 SMITH, RICHARD T., M.D., 117, Haverstock hill, N.W.

1883 SMITH, ROBERT PERCY, M.D., 36, Queen Anne street, W.

1869 SMITH, ROBERT SHINGLETON, M.D., Deepholm, Clifton Park, Bristol.

1866 SMITH, WILLIAM. Melbourne, Australia.

1870 SNOW, WILLIAM VICARY, M.D., Richmond Gardens, Bournemouth.

1888 SOLLY, ERNEST, M.B., Strathlea, Harrogate, Yorks.

1887 SPENCER, WALTER GEORGE, M.S., 35, Brook street, W. (M.G.C. 1894-1900. C. 1896-9.)

1899 SPRIGGS, EDMUND IVENS, M.D., 24, St. Thomas's street, S.E.

1861 SQUIRE, ALEXANDER BALMANNO, M.B., 24, Weymouth street, W.

1890 STABB, EWEN CARTHEW, 57, Queen Anne street, W.

1901 STAINER, E., M.B., 60, Wimpole street, W.

1895 STARLING, ERNEST HENRY, M.D., F.R.S., 40, West end lane, N.W. (C. Com. Sect. C, 1901—.)

1896 STEPHENS, J. W. W., M.D. Address uncommunicated.

1899 STEWARD, FRANCIS J., M.S., 133, Harley street, W.

1900 STEWART, PURVES, M.D., 7, Harley street, W.

1891 STILES, HAROLD JALLAND, M.B., C.M., 5, Castle terrace, Edinburgh.

1897 STILL, GEORGE F., M.D. (HON. SECRETARY, SECT. A), 114, Harley street, W. (C. Com. Sect. A, 1901-3. Sec. Sect. A, 1903—.)

Elected

1879 STIRLING, EDWARD CHARLES, C.M.G., M.D., F.R.S., Adelaide, South Australia [care of Messrs. Elder & Co., 7, St. Helen's place, E.C.].

1884 STONHAM, CHARLES, C.M.G., 4, Harley street, W. (C. 1893-6.)

1896 STRANGEWAYS, T. P., St. John's College, Cambridge.

1902 STRICKLAND-GOODALL, J., M.D., 30, Vanbrugh hill, Blackheath, S.E.

1903 STRONG, WALTER M., "Helstonleigh," Champion park, Denmark hill, S.E.

1875 STURGE, W. A., M.D., 29, Boulevard Dubouchage, Nice.

1867 SWAIN, WILLIAM PAUL, 17, The Crescent, Plymouth.

1881 SYMONDS, CHARTERS JAMES, M.S., 58, Portland place, W. (M.G.C. 1884-91. C. 1886-8. V.-P. 1899-1901.)

1886 TARGETT, JAMES HENRY, M.B., M.S., 19, Upper Wimpole street, W. (M.G.C. 1894-1900. C. 1894-5, 1897-1900. V.-P. 1900-1902. S. 1895-7.)

1870 TAY, WARREN, 4, Finsbury square, E.C. (C. 1881-2.)

1871 **TAYLOR**, FREDERICK, M.D., 20, Wimpole street, W. (M.G.C. 1879-89. C. 1879-81. V.-P. 1897-9.)

1885 TAYLOR, HENRY H., 10, Brunswick place, Hove, Sussex.

1892 TAYLOR, JAMES, M.D., 49, Welbeck street, W.

1902 THIELE, FRANCIS HUGO, M.D., 7, Hampstead lane, Highgate, N.

1891 THOMSON, HENRY ALEXIS, M.D., 39, Drumsheugh gardens, Edinburgh.

1884 THOMSON, JOHN, M.D., C.M., 14, Coates crescent, Edinburgh.

1901 THOMSON-WALKER, J. W., M.B., 8, Cavendish place, W.

1892 **Thorburn**, WILLIAM, B.S., 2, St. Peter's square, and Rusholme Lodge, Rusholme, Manchester.

1872 THORNTON, WILLIAM PUGIN, 35, St. George's place, Canterbury.

1900 THURSFIELD, HUGH, M.D., 45, Weymouth street, W. (C. Com. Sect. A, 1905—.)

1880 TIRARD, NESTOR ISIDORE, M.D., 74, Harley street, W.

1884 TIVY, WILLIAM JAMES, 8, Lansdowne place, Clifton, Bristol.

1901 TODD, CHARLES, M.D., Queensberry Lodge, Elstree, Herts.

1897 TOOGOOD, F. SHERMAN, M.D., The Infirmary, 282, High street, Lewisham, S.E.

1882 TOOTH, HOWARD HENRY, C.M.G., M.D., 34, Harley street, W. (C. 1892-4. M.G.C. 1895-1900.)

1886 TOTSUKA, KANKAI, Tokio, Japan.

1872 **TOWNSEND**, THOMAS SUTTON, 68, Queen's gate, S.W.

1899 TREDGOLD, ALFRED F., London County Asylum, Woodford Bridge, Essex.

1888 TREVELYAN, EDMOND F., M.D., 40, Park square, Leeds.

1902 TREVOR, ROBERT SALUSBURY, M.B., 21, Fitzgeorge avenue, West Kensington, W.

1903 TRITSCH, ISIDOR, Lawn House, Hampstead Heath, N.W.

1851 TROTTER, JOHN W., 4, St. Peter's terrace, York. (C. 1865-9.)

1904 TROTTER, WILFRED BATTEN LEWIS, M.S., 49, Park avenue, Willesden green, N.W.

1895 TROUTBECK, HENRY, M.B., B.C., 151, Ashley gardens, S.W.

1859 **TRUMAN**, EDWIN THOMAS, 23, Old Burlington street, W.

1888 TUBBY, ALFRED HERBERT, M.S., 25, Weymouth street, Portland place, W.

Elected

1867 TUCKWELL, HENRY MATTHEWS, M.D., 64, High street, Oxford.
1858 TUDOR, JOHN, Dorchester, Dorset.
1893 TURNEY, HORACE GEORGE, M.D., M.Ch., 68, Portland place, W.
1858 **TURTLE**, FREDERICK, M.D., Kirkmead, Woodford, Essex.
1880 TYSON, WILLIAM JOSEPH, M.D., 10, Langhorne gardens, Folkestone.

1867 VENNING, EDGCOMBE, 30, Cadogan place, S.W.
1889 VOELCKER, ARTHUR FRANCIS, M.D., B.S., 101, Harley street, W. (C. 1895-7.)

1867 **WAGSTAFFE**, WILLIAM WARWICK, B.A., Purleigh, St. John's hill, Sevenoaks. (C. 1874, 1878-80. M.G.C. 1874-82. S. 1875-7.)
1885 WAKLEY, THOMAS, jun., 16, Hyde park gate, S.W.
1902 WALKER, E. W. AINLEY, M.D., University College, Oxford.
1893 WALKER, NORMAN PURVIS, M.D., 7, Manor place, Edinburgh.
1901 WALLACE, CUTHBERT SIDNEY, 26, Upper Wimpole street, W.
1881 WALLER, BRYAN CHARLES, M.D., Masongill House, Cowan bridge, Kirkby-Lonsdale.
1890 WALLIS, FREDERICK CHARLES, M.B., B.C., 107, Harley street, W. (C. 1898-1901.)
1888 WALSHAM, HUGH, M.A., M.D., B.C., 114, Harley street, W.
1859 WALTERS, JOHN, M.B., Reigate, Surrey.
1892 WARD, ALLAN OGIER, M.D.Edin., 73, Cheapside, E.C.
1903 WARD, EDWARD, M.B., B.C., 21, Park place, Leeds.
1892 WARING, HOLBURT JACOB, M.B., M.S., 37, Wimpole street, W.
1901 WARNER, ALLAN, M.D., Isolation Hospital, Leicester.
1891 WATERHOUSE, HERBERT FURNIVALL, M.D., C.M., 81, Wimpole street, W.
1903 WATERS, W. A. P., M.D., 99, Holywell, Oxford.
1890 WEBB, CHARLES FREKE, M.D., New street House, Basingstoke.
1894 **WEBER**, FREDERICK PARKES, M.D., 19, Harley street, W.
1858 **WEBER**, Sir HERMANN, M.D., 10, Grosvenor street, W. (C. 1867-70. V.-P. 1878-80.)
1864 WELCH, THOMAS DAVIES, M.D. (Travelling).
1894 WELLS, SYDNEY RUSSELL, M.D., 24, Somerset street, Portman square, W.
1892 WESBROOK, FRANK F., M.D., The University of Minnesota, Minneapolis, U.S.A.
1877 WEST, SAMUEL, M.D., 15, Wimpole street, W. (C.1884-6, 1891-3. S. 1889-90. V.-P. 1896-7.)
1891 WHEATON, SAMUEL WALTON, M.D., 10, Restall avenue, Streatham hill, S.W.
1869 WHIPPLE, JOHN H. C., M.D., Royal Army Medical Corps.
1877 WHITE, CHARLES HAYDON, 4, East Circus street, Park row, Nottingham.
1894 **WHITE**, CHARLES POWELL, M.B., Pathological Laboratory, St. Thomas's Hospital, Albert Embankment, S.E. (C. Com. Sect. A, 1903-5.)
1891 WHITE, GILBERT B. MOWER, M.B., B.S., 112, Harley street, W.
1881 WHITE, WILLIAM HALE, M.D., 65, Harley street, W. (C. 1888-90.)

Elected

1886 WHITE, WILLIAM HENRY, M.D., 43, Weymouth street, W.

1868 **Whitehead**, WALTER, 17, Market street, Manchester.

1897 WHITFIELD, ARTHUR, M.D., 21, Bentinck street, Manchester square, W (C. Com. Sect. A, 1905—.)

1869 WILKIN, JOHN F., M.D., M.C., Rose Ash House, South Molton, N. Devon.

1871 WILKINSON, J. SEBASTIAN. Address uncommunicated.

1879 WILLCOCKS, FREDERICK, M.D., 14, Mandeville place, W.

1869 WILLIAMS, ALBERT, M.D. (Travelling).

1858 **Williams**, CHARLES, 48, Prince of Wales road, Norwich.

1866 WILLIAMS, CHARLES THEODORE, M.D., 2, Upper Brook street, W.. (C. 1875-8.)

1881 WILLIAMS, DAWSON, M.D., B.S., 2, Agar street, Strand, W.C. (C. 1893-6.)

1881 WILLIAMS, W. ROGER, Beaufort House, Clifton Down, Clifton.

1900 WILLIAMSON, OLIVER K., M.B., B.C., 55, Upper Berkeley street, W.

1863 WILLIS, FRANCIS, M.D., Asheville, N. Carolina, U.S.A.

1889 WILSON, ALBERT, M.D., 1, Belsize park, N.W.

1888 WILSON, CLAUDE, M.D., C.M., Church road, Tunbridge Wells.

1859 WILSON, EDWARD THOMAS, M.B., Montpelier terrace, Cheltenham.

1891 WILSON, THEODORE STACEY, M.D., C.M., 27, Wheeley's road, Edgbaston, Birmingham.

1861 **Windsor**, THOMAS, Medical Library, Boston, Mass., U.S.A. [care of B. F. Stevens and Brown, 4, Trafalgar square, W.].

1889 WINGRAVE, V. HAROLD WYATT, 11, Devonshire street, Portland place, W.

1874 WISEMAN, JOHN GREAVES, Stranraer, St. Peter's Road, St. Margaret's-on-Thames.

1883 WOODCOCK, JOHN ROSTRON, Darlington Court, North road, Bath.

1883 WOODHEAD, GERMAN SIMS, M.D., 6, Scrope terrace, Cambridge. (C. 1891-3. V.-P. 1898—1900. M.G.C. 1899—1900.)

1879 WOODWARD, G. P. M., M.D., Deputy Surgeon General; Sydney, New South Wales.

1884 WORTS, EDWIN, 6, Trinity street, Colchester.

1903 WRIGHT, ALMROTH EDWARD, M.D., 7, Lower Seymour street, Portman square, W. (C. Com. Sect. B, 1903-5. V.-P., Chairman Sect. B, 1905—.)

1890 WYNNE, EDWARD T., M.B., Gladstone, Queensland.

1884 WYNTER, WALTER ESSEX, M.D., 30, Upper Berkeley street, W.

1872 YOUNG, HENRY, M.B., Monte Video, South America.

1901 YOUNG, HENRY WILLIAM PENNEFATHER, "Dursley," Norbury, S.W.

ANNUAL REPORT OF COUNCIL,

1904–5.

PRESENTED AT THE ANNUAL MEETING, MAY 16TH, 1905.

YOUR Council have to report that during the present session seventeen new members have been admitted to the Society, that ten members have resigned, and that there have been seven losses by death.

The death-roll includes Dr. W. Lee Dickinson, Mr. D. M. Forbes, Dr. T. Gilbart Smith, Dr. C. Kelly, Dr. A. Money, Mr. A. Q. Silcock, Mr. J. Smith Turner.

The total number of members is now 681, of whom a certain number are, under the older regulations, non-resident.

The four Laboratory meetings have been held at the London Hospital Medical School, the Medical School of St. Mary's Hospital, the Royal Army Medical College, and the Medical School of the Middlesex Hospital. To the Pathological Directors of these institutions the Council offers its best thanks.

In July, 1904, an out-of-London meeting was held, on the invitation of Dr. C. J. Martin, F.R.S., the Director of the Lister Institute, at the Elstree Laboratory.

The Council has nothing to lay before the Meeting in regard to the proposed confederation of the London medical societies, as no proposals have yet been formulated by the Committee which is considering this subject.

THE PATHOLOGICAL SOCIETY OF LONDON.

Statement of Receipts and Payments from 14th May, 1904, to 13th May, 1905.

RECEIPTS.	£	s.	d.	£	s.	d.
Petty Cash in hand, 13th May, 1904				2	7	2
334 Subscriptions at £1 1s.				350	14	0
19 Entrance Fees at £1 1s.	19	19	0			
8 Life Composition Fees	31	10	0			
				51	9	0
Transactions—						
Sale of 'Transactions'	50	15	4			
Contributions towards Plates	5	2	0			
				55	17	4
7 Fees for Agenda Notices at 2s. 6d.				0	17	6
Dividends on Consols				20	5	8
				481	10	8
Balance due to Bank				182	6	0
				£663	16	8

PAYMENTS.	£	s.	d.	£	s.	d.
Balance due to Bank—13th May, 1904				125	2	5
Meetings:						
Rent of Rooms	73	10	0			
Attendance at Laboratory Meetings	2	5	6			
Microscopes	16	4	0			
Epidiascope	2	12	0			
				94	11	6
'Transactions':						
Printing, Binding, etc., for Vol. LV	260	16	9			
Illustrations " "	107	12	6			
				368	9	3
Secretariat and Treasury:						
General Printing and Stationery	23	8	2			
Council Notices	0	16	0			
Secretarial Assistance	15	15	0			
Collection of Subscriptions	15	15	0			
Mr. Clarke's Fee	5	5	0			
				60	19	2
Bank Charges				3	2	2
Petty Cash Expenditure				5	1	4
				657	5	10
Petty Cash in hand				6	10	10
				£663	16	8

Audited and approved, May 15th, 1905.

P. H. PYE-SMITH, M.D., F.R.S., *Treasurer.*
S. G. SHATTOCK, *Hon. Secretary.*

S. N. BRUCE,
T. W. P. LAWRENCE, } *Auditors.*

LIST OF COMMUNICATIONS

MADE TO THE SOCIETY DURING THE SESSION 1904-5.

		PAGE
1.	A research into the heat regulation of the body by means of an investigation of death temperatures — E. M. Corner and J. E. H. Sawyer	1
2.	Sarcomata of the alimentary canal — E. M. Corner and H. A. T. Fairbank	20
3.	Emphysematous gangrene — L. S. Dudgeon and P. W. G. Sargent	42
4.	Methods of comparing abnormal and normal tissues — S. G. Shattock and C. F. Selous	53
5.	Results of vasectomy and castration upon the appearance of secondary or external sexual characters — S. G. Shattock and C. G. Seligmann	57
6.	The results of castration and vasectomy upon the prostate gland in the enlarged and normal condition — C. S. Wallace	80
7.	Unusual form of consolidation of left lung occurring in a case of occlusion of bronchus by blood-clot — T. J. Horder	106
8.	Simultaneous occurrence of filarial and malarial parasites in the blood — C. F. Selous	113
9.	Acute lymphocythæmia — L. S. Dudgeon	114
10.	Bacillus enteritidis in cow's milk — E. Klein, F.R.S.	132
11.	Acid media in isolation of *B. pestis* — W. C. C. Pakes and F. H. Joseph	135
12.	Fugent—a new stain — F. H. Joseph	137
13.	Cyst in connection with ampulla of Vater — R. S. Trevor	138
14.	Toxæmic jaundice — J. F. H. Broadbent	145
15.	Recent work on proteid chemistry — W. D. Halliburton, F.R.S.	158
16.	Parasites of smallpox, vaccinia, and varicella — W. E. de Korté	172
17.	Schistosoma Cattoi — J. Catto	179
18.	Relation of adrenals to the sexual organs — W. Bulloch and J. H. Sequeira	189

PAGE

19. Tumour of adrenal associated with precocious sexual development — C. E. Adams — 208
20. Obliterative arteritis — W. P. S. Branson — 212
21. Obliterative arteritis — E. Michels and F. P. Weber — 223
22. The vitality of the typhoid bacillus in shellfish — E. Klein, F.R.S. — 231
23. Experiments on the grafting of the thymus gland in animals — L. S. Dudgeon and A. E. Russell — 238
24. The chemical examination of the gastric contents with an accurate clinical method of determining the active hydrochloric acid present — W. H. Willcox — 250
25. Carcinoma of the cardiac orifice of the stomach, involving the œsophagus — J. Fawcett — 259
26. The etiology of carcinoma — K. W. Monsarrat — 262
27. A prehistoric or predynastic Egyptian calculus — S. G. Shattock — 275
28. Suppurative periostitis following typhoid fever — W. H. Battle and L. S. Dudgeon — 291
29. A phosphatic vesical calculus formed on an ear of wheat-straw in a male — W. H. Battle — 296
30. A case of subacute atrophy of the liver — S. G. Scott — 298
31. A case of asymmetrical congenital malformation of the lower extremities — H. Rundle — 307
32. On secondary carcinomatosis of bones and osteoplastic changes connected with them — F. H. Thiele — 314
33. A case of squamous-celled carcinoma of the finger, associated with frequent and prolonged exposure to X rays — A. G. R. Foulerton — 327
34. Broncho-pneumonia with multiple cavities — J. M. Bernstein — 330
35. Enquiry into the opsonic content of the blood-serum in healthy individuals and in patients affected by lupus — W. Bulloch — 334
36. Some experiments in connection with "stimulins" — W. B. Leishman — 344
37. Myasthenia gravis — E. F. Buzzard — 355
38. On the occurrence of squamous epithelium in carcinoma of the body of the uterus — R. D. Keith — 365
39. On the nature of the vesicular structures found in malignant growths, and sometimes known as Plimmer's bodies — C. E. Walker — 372
40. On the behaviour of leucocytes in malignant growths — J. E. Farmer, F.R.S., J. E. S. Moore, and C. E. Walker — 377
41. The *rôle* of the lymphocyte — J. B. Cleland — 381

REPORTS OF COMMITTEES.

PAGE

Report upon Mr. K. W. Monsarrat's communication on the etiology of carcinoma 272

LIST OF PLATES.

	TO FACE PAGE
I. Acute lymphocythæmia. (L. S. Dudgeon) . .	120
II. Myasthenia gravis. (E. F. Buzzard) . . .	362
III. The nature of the vesicular structures in carcinoma, sometimes known as Plimmer's bodies . .	380

LIST OF FIGURES IN THE TEXT.

		PAGE
1.	Emphysematous gangrene (L. S. Dudgeon)	51
2.	Method of comparing abnormal with normal tissues (S. G. Shattock and C. F. Selous)	56
3—9.	Acquirement of secondary sexual characters (S. G. Shattock and C. G. Seligman)	60—75
10—18.	Results of castration and vasectomy upon the prostate gland	87—105
19—22.	Consolidation of lung (T. J. Horder)	107—110
23.	Simultaneous occurrence of filarial and malarial parasites in the blood (C. F. Selous)	113
24—27.	Acute lymphocythæmia (L. S. Dudgeon)	122—125
28—33.	Cyst in connection with ampulla of Vater (R. S. Trevor)	140—144
34—36.	Toxæmic jaundice	147—153
37—39.	Schistosoma Cattoi (J. Catto)	183—185
40.	Relation of adrenals to sexual organs (W. Bulloch and J. H. Sequeira)	193
41, 42.	Obliterative arteritis (W. P. S. Branson)	217
43, 44.	Obliterative arteritis (E. Michels and F. P. Weber)	226, 227
45, 46.	Grafting of thymus gland in animals (L. S. Dudgeon and A. E. Russell)	248
47.	Etiology of carcinoma (K. W. Monsarrat)	265
48—50.	A prehistoric calculus (S. G. Shattock)	281—288
52.	Calculus on ear of wheat-straw (W. H. Battle)	297
53, 54.	Subacute atrophy of liver (S. G. Scott)	302, 303
55—57.	Malformation of lower limbs (R. Rundle)	308—312
58.	Carcinomatosis of bone (F. H. Thiele)	326
59.	Broncho-pneumonia with multiple cavities (J. M. Bernstein)	331
60.	Squamous epithelium in carcinoma of body of uterus (R. D. Keith)	369
61.	Leucocytes in malignant growths (J. E. Farmer, F.R.S., J. E. S. Moore, and C. E. Walker)	380
62—64.	The *rôle* of the lymphocyte (J. B. Cleland)	382—384

REPORT.

SESSION 1904–1905.

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1. *A research into the heat regulation of the body by means of an investigation of death temperatures.*

By E. M. Corner and J. E. H. Sawyer.[1]

Summarium.

In duas partes divisum est hoc opusculum. In alterâ parte de caloris corporis mutationibus, quas inter duodecim ultimas vitæ horas moribundi subeunt, disputamus ex comparatione duorum milium et quingentorum (2500) exemplorum quæ in tabulis in Sancti Thomæ nosocomio conservantur.

In alterâ parte, his exemplis collatis, explicare conamur quomodo calor corporis sani temperetur, et quas ob causas morbo affecti calorem aut minorem aut majorem concipiant.

Haec explorata habemus. Ex centum exemplis eorum

[1] 'Proceedings of the Royal Society, London,' vol. lxxiii, 1904.

qui a chirurgis curati sunt, quadraginta nonem (49 per cent.), et ex eodem numero eorum qui a medicis curati sunt, undeviginti (19 per cent.) ita afficiuntur ut calor corporis aut minor aut major uno et dimidio gradu (Fahrenheit 1·5°) inter duodecim ultimas vitæ horas fiat.

Quorum, exemplis centum item sumptis, septuaginta quattuor (74 per cent.) accretionem, viginti sex (26 per cent.) deminutionem caloris monstrant.

Satis apparet ex chartis accurate descriptis, quantum et sexus et ætas et varia morborum genera valeant.

Præterea accretioni caloris magis obnoxia sunt corpora eorum quos morbi breviores, ad deminutionem proclivia eorum quos morbi diutini, oppresserint.

Has autem mutationes multo sæpius monstrant pueri qui minus quinque annos nati sunt, quam adulescentes aut seniores.

Ex iis exemplis in parte secundâ digestis, et ex eo quod de his mutationibus caloris jam cognoscimus, hanc rationem de causis, unde pyrexia fit, exponimus. Oriri potest pyrexia ex duabus causis—(*a*) quod auctus est calor propter actionem centrorum thermogeneticorum quæ, in chordâ spinali sita, non obedient centro superiori in cerebro sito; (*b*) quod, propter actionem centri thermolytici debilitatam, minus cito calor dissipatur: namque haec duo centra superiora (nempe centrum thermogeneticum tonicum et centrum thermolyticum) iis toxinis quæ morbus ipse in corpore affecto genuit, aut debilitantur aut resolvuntur (vide Figuram p. 19). Hoc probato, sequitur ut duo nervorum centra, dum sanum quodlibet corpus sit, temperaturam constantem sustineant, quorum alterum accretionem, alterum deminutionem caloris moderetur.

The fact has long been known that, in many forms of disease, variations of the bodily temperature occur as death approaches. Our knowledge of such variations is limited to certain apparently sporadic cases. Hitherto, no attempt has been made to ascertain the special class of disease in which such deviations occur most frequently, nor has the subject been examined in a scientific light, so as to bring these death temperatures in line with the present knowledge of the mode of production of pyrexia. It is towards this latter object that this inquiry has been directed. Further encouragement to bring forward this new source of knowledge is given by Sir John Burdon Sanderson, who says "the subject (of pyrexia) is one in respect of which results as valuable can be obtained by clinical investigation as by experiments on animals."*

This communication has been divided into two parts. In the first part, a general account is given of the bodily temperature immediately preceding death, and of the variations which are seen in these thermometric records. A series of problems are shown, in order to ascertain, where possible, the different factors which may influence the variations in the death temperature. The figures quoted are, in all cases, the absolute minimum, as numbers of these cases have to be rejected for many reasons—for example, those in which tepid sponging has been employed, and others where the records are incomplete. In the second part, an attempt is made to ascertain the possible influences which may cause such variations in the bodily temperature, and to explain, from a study of these changes, the mechanism by which the temperature of the body is regulated in health, and the reasons for which deviations from the normal occur in disease.

Part I.

As the fatal result approaches, the curve on the temperature chart may exhibit several changes. In 49 per cent. of surgical and in 19 per cent. of medical cases, a definite change of over 1·5° F. occurs during the twelve hours immediately preceding death. These figures are the absolute minimum for about 2500 consecutive cases which have been collected from the records of

[1] Clifford Allbutt, 'System of Medicine,' vol. i, p. 152.

St. Thomas's Hospital. In instances where no such sudden change occurs, the temperature may remain at about the same level, but the more usual procedure is for it to fall slowly and steadily. On the other hand, it is not common for the bodily temperature to rise slowly, for, when an elevation occurs at all, the change is generally a sudden one. The character of the temperature charts as death approaches is naturally affected by the types of fever from which the patients may be suffering, such as remittent, intermittent, etc. The influence of these fevers cannot be eliminated, and it is an interesting point that such cases frequently show a very decided variation in the character of the temperature near the fatal termination. The performance of tepid sponging, or the exhibition of antipyretic drugs, just before the death of the patient, renders the chart valueless for this research. For these, and similar reasons, many variations of temperature have been necessarily neglected.

There are other changes in the temperature charts which have to be considered in these investigations. Sometimes, about twenty-four hours before death, the temperature falls suddenly, anything from 1° to 5° F., and then rises rapidly, and at this point death may occur. On the other hand, the fatal result may be postponed, and, after the temperature has reached its maximum, defervescence may begin again. Such fluctuations as these are more commonly found among surgical than among medical cases. The following is a good example of these changes: A baby girl, aged 7 weeks, was severely burnt, and died on the fifth day; the temperature during the last thirty-six hours of life represented these variations; it fell 4·3°, rose 6·4°, falling again 4·2°. Again, in a woman, aged 28 years, who suffered from general peritonitis and appendicitis, there was a fall of 4° in the temperature, followed by a rise of 8°, when death occurred. These early deviations of the temperature begin about twenty-four hours before the death of the patient, and may exaggerate either the death rise or the death fall, or may mask them altogether.

Of the 2500 cases which were examined, 1305 were medical cases, the remainder, 1195, being surgical. Changes in the bodily temperature of over 1·5°, occurring during the last twelve hours of life were found in 34 per cent. of all the records examined, in 49 per cent. of surgical, and in only 19 per cent. of medical

cases. On account of this great difference of 30 per cent. the two lists of cases have been kept separate, although in many instances they overlap. The explanation of the difference which is found between the medical and surgical cases has to be sought for in the other particulars.

Of the variations found among the fatal medical cases, 75 per cent. were rises of temperature, and 25 per cent. falls. For the surgical cases, the corresponding percentages were 73 and 27, the two classes agreeing very closely. Elevations of temperature occurred in 26 per cent. and falls in 8 per cent. of all the cases examined.

The relative proportions of male to female deaths were also investigated, and the following figures were obtained :

Medical cases.

Proportion of male to female deaths during the same period.....	1·75	male to	1	female.
Ditto, showing death rise of temperature...	1·57	„	1	„
Ditto, showing death fall of temperature...	1·45	„	1	„

Surgical cases.

Proportion of male to female deaths during the same period.....	1·63	male to	1	female.
Ditto, showing death rise of temperature...	1·75	„	1	„
Ditto, showing death fall of temperature...	1·39	„	1	„

The following deductions may be made from these figures, indicating lines along which an explanation of the phenomena may be sought.

In surgical cases males are more apt to show a death rise ; females, on the other hand, show a marked tendency to death falls. In medical cases the difference is not so marked, but female patients are relatively more liable to death variations of temperature than are male. A fall of temperature in both medical and surgical cases is more common in females than in males.

There is one point on which medical and surgical cases differ from each other, which is, that in the latter deaths due to injury are included. As to the actual cause of death in disease

and in injury the difference is not so great, but, as will be seen in the following table, the death temperatures vary considerably in one important point in the two classes. Only the surgical cases are here considered:

Proportion of deaths due to disease and injury	1·88	disease to	1 injury.
Ditto, showing death rise	1·84	„	1 „
Ditto, showing death fall	3·29	„	1 „

These figures show that rises in the bodily temperature, just before death occurs, are found to be present in fairly equal proportion in patients dying from disease and from injury. Falls of temperature, however, are very much more common in patients suffering from disease. The following table shows the same proportions in percentages:

	Disease.	Injury.
Proportion of death changes to total	51·7 per cent.	46·0 per cent.
Proportion of death rises to total	36·5 „	37·3 „
„ „ falls „	15·2 „	8·7 „

From this table it would appear that changes of temperature as death approaches occur less frequently in injuries than in disease, and that this difference is due to the comparative rarity of death falls in the former. The rises of temperature are present in equal proportion in the two classes of cases.

In the charts on the page opposite an attempt is made to show the amount and frequency of the various deviations of temperature:

The following conclusions may be drawn from Charts 1 and 2:

1. That death rises of temperature are naturally larger than death falls.

2. That small variations of temperature are more common than large.

3. That death rises are comparatively rare over 5°, more so over 6°.

4. That death falls are comparatively rare over 4°, more so over 5°.

5. That the variations of temperature in the medical and

surgical cases agree fairly well, although death rises in medical cases are relatively more common from 3° to 4°.

CHART 1.

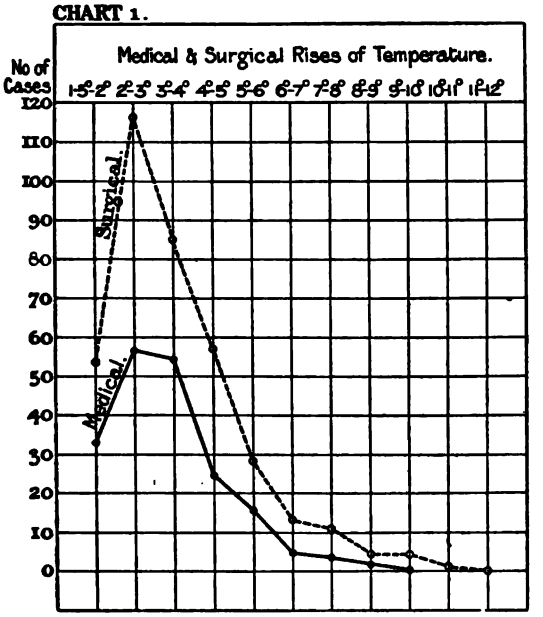
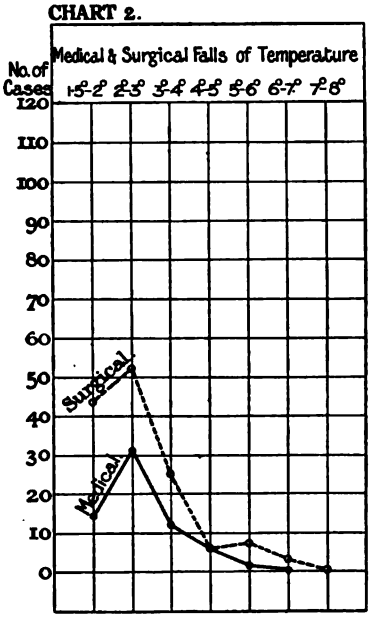


CHART 2.



6. That death rises are more frequently of greater magnitude in surgical than in medical cases.

Charts 3 and 4 show the actual temperature at the time of

CHART 3.

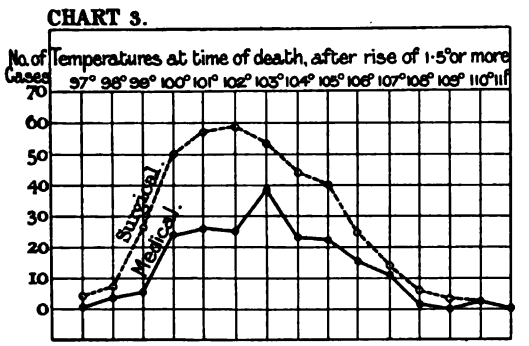
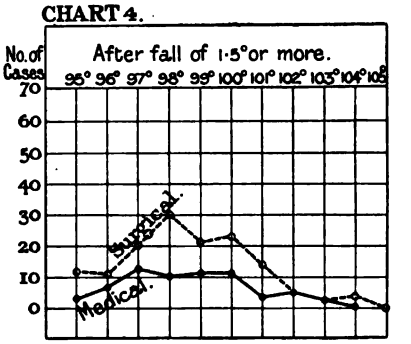


CHART 4.



death (or rather, the last recorded while life was still present) in cases in which there had been a previous thermometric variation of over 1·5°.

From these charts the following deductions are made:

1. That there is very little difference between medical and

surgical cases as regards the final temperature, whether it be preceded by a rise or by a fall.

2. That when death rises occur the final temperature is most frequently between 101° and 103°, but quite commonly ranges from 100° to 106°.

3. That after death falls the most common final temperature is between 97° and 100°, but falls as low as 95° are fairly frequent. The high temperatures which are recorded under the death falls are due to the previous rises of temperature, just as the low temperatures under the death rises are due to previous falls.

The variations of the temperature of the preagonistic stage are considered in the following table with respect to the duration of the illness as estimated roughly by the length of the period between admission to the hospital and the death of the patient. This method by no means tells correctly the duration of the illness; but by no other way can it be estimated on account of the histories being so unreliable. It was decided in consequence to accept the above method only in surgical cases, as indicating fairly well in this class the state of affairs:

Duration of stay in hospital.	Rises.		Falls.	
1 day	72		21	
2 days	57		12	
3 „	18		8	
4 „	21	1st week, 236	6	1st week, 68
5 „	41		12	
6 „	14		7	
7 „	12		2	
7 „ to 10 days	29	2nd week, 63	12	2nd week 22
10 „ „ 14 „	34		10	
14 „ „ 21 „	25		18	
21 „ „ 28 „	19		9	
1 „ „ 2 months	35		16	
2 „ „ 3 „	5		0	
3 „ „ 4 „	4		4	
Over 4 „	4		2	

Owing to the obvious errors that enter into the composition of such a table, it was decided not to continue it into details. The nature of the disease would be expected to affect the death

changes of temperature far more than the mere duration of the illness would. But one point stands out in the above table, namely, that the shorter the illness the greater the number of cases in which variations of temperature are found. How far this is relative or absolute has not been calculated, for the reasons which have just been given. The largest number of rises are found in short illnesses; but the corresponding statement, as founded on the above table, which is composed only of surgical cases, does not hold good for the falls of temperature, but, as will be seen later, there is distinct evidence that sudden depressions of temperature as death approaches occur frequently in diseases of long duration.

The disease which brings about the fatal termination may be regarded as the most important factor in causing the changes of temperature which occur as death approaches. The influence of the disease upon the character of the pyrexia, when death is associated with a rise of the bodily temperature, has already been slightly indicated. The following diseases are those in which the greatest variations were found:

Medical cases.

Rise of 8°.—Acute yellow atrophy of the liver.

7°.—Septic meningitis, tubercular meningitis, typhoid fever (preceded by hæmorrhage and a fall of temperature).

6°.—General tuberculosis, cerebra hæmorrhage, septic meningitis, peritonitis, marasmus and diarrhœa.

5°.—Peritonitis; intussusception, preceded by a fall (two cases); general tuberculosis (three cases), pneumonia (two cases), diphtheria, chronic renal disease, carcinoma of the liver, intestinal obstruction, carcinoma of the small gut, hemiplegia, ulcerative endocarditis, acute yellow atrophy.

The list of diseases for the smaller elevations of temperature is too long for reproduction. Two points are clearly seen from this table—that in severe toxic diseases a large rise of temperature is common, whilst in heart disease it is very rare.

Surgical cases.

Rise of 10°.—Fractured base of skull.
9°.—Fractured spine, fractured skull, burn.
8°.—Strangulated hernia and peritonitis, tetanus, pyæmia.
7°.—Septicæmia, intestinal obstruction and peritonitis, fractured vault of skull, fractured base, burn (two cases), pyæmia, suppurative nephritis, septic bronchopneumonia.
6°.—Peritonitis, various causes (five cases); meningitis (two cases), burn, scald, spina bifida, imperforate anus, gluteal abscess.

From this list the following conclusions may be drawn:

1.—That injuries to the head and spine generally give rise to high death changes of temperature. This may be emphasised by the low temperatures which precede the final rise and which are the result of the shock caused by the injuries. Such a condition is frequently found in those patients who succumb within twenty-four hours after admission to the hospital.[1]

2. That the following diseases are the most frequent in taking the prominent places among the death rises of temperature:

Head injuries: 10°, 1; 9°, 1; 8°, 1; 7°, 2; 6°, 1; 5°, 5—11 cases.
Spinal injuries: 9°, 1; 6°, 1; 5°, 1—3 cases.
Burns: 9°, 1; 7°, 2; 6°, 1; 5°, 6—10 cases.
Scalds: 6°, 1; 5°, 1—2 cases.
Meningitis: 6°, 2—2 cases.

3. Besides the above, death in cases associated with a rise of temperature is most always due to some form of poisoning by septic organisms. Thus the remainder of the list of cases with a death rise of 5° or more can be summed up as follows: Peritonitis, septicæmia, pyæmia, septic meningitis, septic bronchopneumonia, suppurative nephritis, cellulitis. It appears from this that, besides the injuries already mentioned, a septic process

[1] Sawyer, "The Temperature of Coma," 'Brit. Med. Journ.,' December 26th, 1903.

causes the death rise in almost all cases. The predominance of this process in causing death in surgical cases probably accounts for the difference in the numbers of the death variations in medical and surgical cases.

Medical cases.

Fall of 5°.—Phthisis.

4°.—Typhoid fever, hæmorrhage (two cases); intestinal obstruction, broncho-pneumonia, cardiac failure, phthisis (two cases).

3°.—Diphtheria, mitral disease, cirrhosis of the liver, hæmorrhage, cardiac failure, bronchitis, myelitis, pneumonia, chronic renal disease (two cases), tubercular meningitis (two cases), phthisis (two cases).

This list shows that large falls of temperature occur in diseases of long duration, such as phthisis; the absence of diseases of the central nervous system and the comparative frequency with which cardiac affections is found are also striking facts.

Surgical cases.

Fall of 6°.—Intestinal obstruction, cyst of ovary, erysipelas.

5°.—Sarcoma of pelvis, carcinoma of rectum and obstruction, compound depressed fracture of vault, scald, septicæmia, pyæmia, abscess.

4°.—General peritonitis (two cases), pyæmia (two cases), tubercular laryngitis and phthisis, epithelioma of tongue, sarcoma of tibia.

3°.—Injury to chest and bronchitis, fractured ribs, sarcoma of face and scalp, suppurative nephritis, erysipelas, pyæmia, sarcoma of neck, cellulitis, imperforate anus, burn, cut throat, ruptured gut.

The general absence of injury and the great preponderance of sepsis are striking features in the above list. Some of the falls of temperature are dependent upon the shock following a surgical operation.

The distribution as regards the age of the patients, with variations of temperature, is shown in the two charts below:

The deductions which may be made from Charts 5 and 6 are:

1. That the variations in the temperature as death approaches are more frequent in children under the age of 5 years than at any other period of life.

2. That between the ages of 5 and 10 years there is a marked decrease in the frequency of the variations of temperature.

CHART 5.

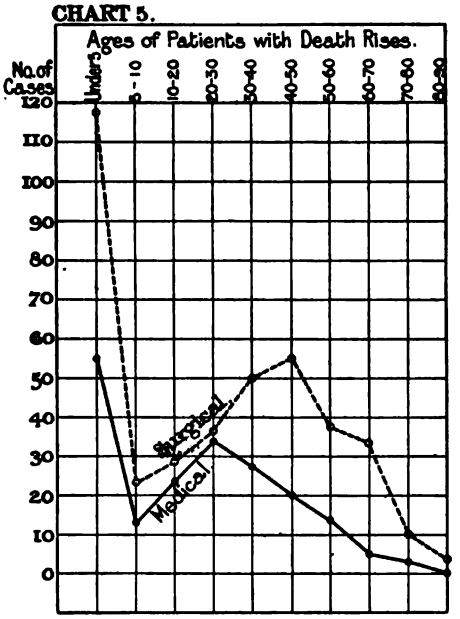
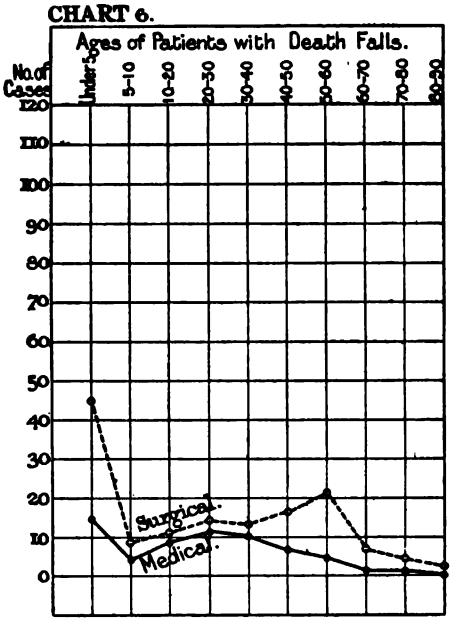


CHART 6.



3. That between the ages of 20 and 50—that is, during the most active period of life—variations of temperature more commonly occur than at any other period, except in children under 5 years of age.

4. That rises and falls of temperature are relatively of the same frequency to each other at all periods of life.

Part II.

As in so many physiological controversies, the various theories fall under two headings—firstly, the inanimate, in which the

question is examined from the point of view of chemistry, physics, etc.; and secondly, the animate, which deals with the phenomena of living tissues. So also in the subject of pyrexia there is found a similar condition of affairs. The inanimate theories deal with the ratio of production and the loss of heat to each other, the disturbances of which must lead to change of temperature. The first question to be discussed is how the approach of death affects the interchange.

(*a*) It seems hardly rational to expect that the capacity for the production of heat will increase as the body approaches death. The physiological processes of the body become less and less active until they cease. In diseases such as tetanus, in which tremendous convulsions take place, there must be an enormous production of heat, and yet in this condition there is usually no pyrexia. Towards death the frequency of the convulsive seizures may somewhat subside, and after this change there is often an elevation of temperature. Under such conditions the increase in temperature may be brought about by an excess of heat production over heat loss. The majority of the other cases of death rises of temperature cannot be accounted for in this manner. Again, curari causes muscular paralysis by suspending the activity of the neuro-muscular system, and as a result a fall in the temperature of the body occurs; but during the convulsions which are first caused by the drug the temperature rises.[1]

With regard to the falls of temperature at the approach of death, an explanation which is very tempting to urge is that with the loss of the activity of the bodily processes a diminution also occurs in heat production. In support of this view may be put forward the fact that the greater the duration of the illness, the more frequently is there a sudden depression of temperature. For, in diseases which are of long duration, the capacity of the organism for heat production is much more likely to become diminished than in illnesses which last only a short time.

(*b*) The heat loss as death approaches must be diminished in almost all cases by the slowness of the circulation, shallowness of respiration, suppression of urine, etc. These changes would

[1] Pembrey, 'Text-book of Physiology,' 1898, edit. by Schäfer, vol. i, p. 841; Bernard, 'Leçons sur la Chaleur Animale,' 1876, p. 157.

tend to cause a rise of temperature. Such an event would naturally be expected to be more frequent when the illness is short and the organs of heat production are not worn out by work under a prolonged strain. And, as has been pointed out above, if the disease should be of long duration, a fall of temperature rather than a rise would be expected to occur. The reason for this supposition is that as death approaches in long illnesses, there must presumably be a considerable diminution of heat production, which is not counterbalanced by the small reduction of the heat lost at the surface. The investigations in the first part of this paper support these ideas, since they seem to show that rises in the bodily temperature occur more frequently in short diseases and falls of temperature in those of longer duration.

The animate factor in pyrexia is chiefly that of the action of the central nervous system. "The nervous system exercises a control upon the loss of heat by means of the vaso-motor system, which regulates the amount of blood in the deep and the superficial parts of the body, and by the respiratory centre, which controls the frequency and depth of respiration; upon the production of heat through the nerves, which control the activity of the tissues, chiefly the muscles."[1] The heat formation in a tissue is probably not under the control of that tissue itself, but its thermogenetic function is governed by its proper segment of the spinal cord. The nervous centres cannot of themselves produce heat: they can only govern the manufactories.

As the brain centres exercise a tonic control over the spinal centres, which are in connection with the reflexes, sphincters, etc., so, in a similar manner, the higher centre or centres of the brain may hold in check the lower centres in the spinal cord, which give the tissues their power of heat production. The brain centres are the last to be evolved in the history of animal life, and it may be urged that they are the most complex, and therefore the most easily thrown out of gear. For this reason a generally acting death agent such as a toxic condition will affect and inhibit the action of the higher centres before or to a greater extent than it will damage the lower. Whenever the higher centre is cut off from the lower, the latter becomes exaggerated in its action. This is well seen in the spastic condition when the reflexes, etc., are exaggerated. In a similar way, with

[1] Pembrey, Schäfer's 'Text-Book of Physiology,' 1898, vol. i, p. 854.

the commencement of the dissolution of the higher centres, a death elevation of temperature may be expected to result.

The fallacy in reasoning from the above analogy is that, in the one case, the facts deal with a reflex centre, and in the other, as far as is understood, with an automatic. How far these differ in regard to their relation to the higher centres it is impossible to say, but one can instance the acceleration of the automatic and rhythmic centre of the heart when the inhibitory control of the vagus is cut off.

An important fact which this investigation shows is that, as death approaches, there is a tendency for a sudden rise in the bodily temperature. In about 2500 medical and surgical cases an elevation of temperature of over 1·5° was found in 26 per cent., or just over a quarter of all the cases, while a fall occurred in 8 per cent. only. The percentage of rise of temperature in surgical cases is 37, and in medical 15. It is a most remarkable fact that this sudden elevation of temperature is observed to take place so frequently in surgical cases, in over a third of all the cases examined, and that this change should be found to occur more than twice as often in them as in medical cases. As the surgical diseases in these records are of shorter duration, as a rule, than the medical, the tissues in consequence have not been so long exposed to abnormal conditions, and so their heat-producing functions are less likely to be impaired. Again, falls of temperature are proportionally much more common in patients dying from disease than from injury. It may be presumed, therefore, that the loss of control of the nerve centres in an exhausted organism only occasionally results in an elevation of the bodily temperature, whereas with less exhausted tissues an increase in the animal heat occurs. From these considerations it would appear that heat production is constantly in excess, and that in consequence of this, the organism must exercise some tonic control over the process in order to keep its temperature at a constant level.

The idea of the thermogenetic control of the higher centre over the lower gives point to the modified and accepted view of Liebermeister that, "in consequence of the injurious action of the fever-producing cause, the organism loses its power of keeping itself at the normal temperature."[1] The poison will, unless it has special affinities, affect the higher and the more complex

[1] Burdon Sanderson, Allbutt's 'System of Medicine,' vol. i.

centres before the lower. Hence the "spastic" over-production of heat which may result in fever. The great frequency of death rises of temperature in cases of head injuries, some spinal injuries, meningitis, brain diseases, etc., emphasises the possible removal of the controlling function of the higher centres. On the other hand, it should be remembered that many of the patients had pyrexial temperature charts, it may be for some days before the preagonistic variations of temperature occurred. The regulation of the bodily heat in these cases was already partially out of the control of the nervous system, and the further elevation of temperature during the last twelve hours of life may be thought to be due to an increasing loss of this control on the part of the organism.

In small animals, after section of the spinal cord in the cervical region, the temperature falls rapidly; in larger animals, such as dogs, if kept in an envelope of non-conducting material in an ordinary room, the temperature of the body rises to above that of fever, but without clothing the temperature rapidly falls until the animal dies in collapse.[1] In man, according to Sir Benjamin Brodie, section of the spinal cord in the cervical region causes pyrexia, but very discordant results have been obtained by other observers in cases with similar injury to the nervous system. Dr. Pembrey's explanation of these contradicting results seems to be the correct one. He says: "The section of the spinal cord high up in the cervical region abolishes the power of regulating temperature. When the patient is exposed even to moderate cold, his temperature falls owing to the increased loss of heat and to the diminished production of heat. On the other hand, if the weather be hot and the patient be too well covered with bed-clothes, his temperature rises and may reach a dangerous height, owing to the diminished loss and the increased production of heat in the body. In the paralysed man the production of heat rises and falls *with* the external temperature."[2] And Sir John Burdon Sanderson writes: "Section only shows the abnormal facility with which the body yields to the influence of outside conditions."[3] It might be urged that the variations of tempera-

[1] Burdon Sanderson, "On the Process of Fever," 'The Practitioner,' vol. xvi, 1876, p. 426.

[2] Pembrey, Schäfer's 'Text-Book of Physiology,' 1898, vol. i, p. 862.

[3] Burdon Sanderson, "On the Process of Fever," 'The Practitioner,' vol. xv 1876, p. 428.

ture, just before death, are due to a similar condition; but obviously this cannot be the case, for after section of the spinal cord many other factors arise which are not present in those patients who suffer from no such lesion of the nervous system. After section, the respiratory movements are altered in character, and respiration is entirely performed by the action of the diaphragm, and in consequence there is less loss of heat through this channel. Again, the muscles are paralysed, and, therefore, cannot produce the normal amount of heat, while the sweat-glands are no longer active, and thus less heat is lost by the evaporation of moisture from the external surface. For these reasons alone the death variations of temperature found in the patients who are considered in the first part of this paper are in no way analogous to the changes which occur after section of the spinal cord in the cervical region.

Arguing from the supposition that the higher centres have a tonic control over the lower, it is to be expected that stimulation of the former should lead to a still further control and diminution of the action of the latter. In this way falls of temperature may be caused. How far a toxic agent will stimulate it is difficult to say. It is possible that some antipyretic drugs may act in this way, such as quinine and salicylic acid. Other substances seem too powerful to stimulate and would appear to paralyse the higher centres. Smaller doses of the poison, however, may act as a stimulant, first to the higher and then to the lower centres, the former being affected before the latter. It may be that for this reason there is a slow rise of temperature in some diseases, while in others of more severe onset there is a sudden elevation of temperature which may be due to paresis of the higher centres.

Septic conditions frequently show changes of death temperature, which may be the result of:

1. Stimulation of the higher centres over the lower, producing fall of temperatures.

2. Paralysis of the higher centres over the lower, producing rise of temperatures.

3. Simultaneous paralysis of higher and lower centres, producing no change.

4. Special poisons may affect higher and lower centres differently.

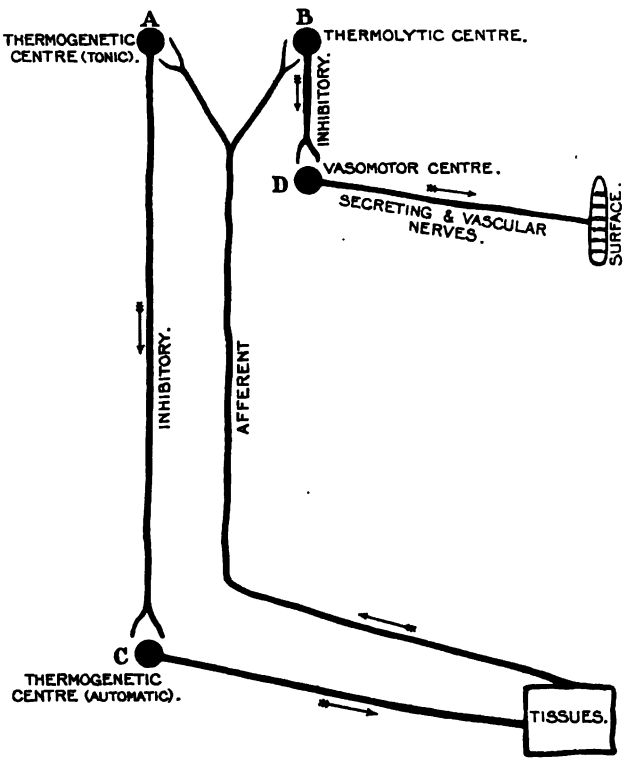
There seems to be some evidence, therefore, in favour of the view that a higher centre in the brain controls the thermogenetic centres in the spinal cord, but it does not follow, when there is an increased heat production through the removal of this control, that there must necessarily be pyrexia. An increase in the loss of heat may keep the temperature at the normal level. In patients, however, who are dying there is a tendency for the amount of heat lost to be diminished, the evidence for which has been pointed out above. Besides this natural tendency, means are constantly employed to prevent falls of temperature in the frail, by increasing the amount of bed-clothes, by using hot bottles, by bandaging the limbs before operation, etc. This slight diminution in the amount of heat lost may suffice to prevent the temperature of the body falling, but it would hardly be sufficient to raise it many degrees without some increase in heat production. From these considerations it would appear that the variations in bodily temperature as death approaches must be dependent in many instances upon the increased amount of heat production and not upon the diminution of heat lost. As these variations are so constant, there is an indication that, although the centre which controls thermolysis, heat-loss, may be the chief factor in keeping the body at a normal temperature, yet the centre which controls thermogenesis plays a more important part than has lately been attributed to it.

The thermolytic centre probably has an inhibitory effect upon the vaso-motor centre, *i. e.* over vaso-constriction, in a similar manner, we think, to the action of the upper thermogenetic centre upon the lower in the spinal cord. As the lower thermogenetic centres tend to exaggerate the amount of heat produced in the tissues, so the vaso-motor centre by constricting the vessels tends to diminish the amount of heat being lost, the latter effect being counterbalanced by the inhibitory action of the thermolytic centre. The action both of the lower thermogenetic centre and also of the vaso-motor centre, when not controlled by the higher centres, seems to be that of raising the bodily temperature.

Whatever effect the fever-producing agent has upon the controlling power of the higher thermogenetic centre, it will probably act in a similar manner upon the thermolytic centre. If this should be the case, paralysis or weakening of the functions

of these two centres would result in a much higher elevation of temperature than if the thermogenetic controlling centre in the brain alone was affected.

The following diagram shows the hypothetical relationship of the different nerve centres which take part in the regulation of the bodily temperature. The afferent path from the surface to the vaso-motor centre has been left out for the sake of clearness.



If A or B be paralysed or weakened, there is a tendency to pyrexia; if both A and B be paralysed or weakened, there is a tendency to hyperpyrexia; if C or D be paralysed or weakened, there is a tendency to a fall of temperature.

If A or B be stimulated, there is a tendency to a fall of temperature; if both A and B be stimulated, there is likely to be an extreme fall of temperature; if C or D be stimulated, there is a tendency to pyrexia.

From these considerations, and from the facts which have been

elicited by a careful study of the death variations of temperature, the following theory for the causation of pyrexia seems to present itself. Pyrexia is due to two factors—to an augmented production of heat owing to the activity of the thermogenetic centres in the spinal cord being no longer perfectly controlled by the higher centre in the brain, and to a diminished loss of heat owing to the weakening of the functions of the thermolytic centre; the power of the two higher centres being weakened or paralysed by the morbid products or toxines of the affection from which the organism is suffering. In other words, normal temperature is preserved by a mutual see-saw action of these centres—the thermogenetic and the thermolytic.

We recognise fully that, for a more perfect understanding of death temperatures it is necessary for the observers to examine the patients for themselves, and not to trust to records, however many or accurate they may be, so that they can note in each case the changes in the skin, the circulation, the respirations, etc., concurring with the variations of the bodily temperature. Nevertheless, we venture to put forward our investigations and views, not as physiologists, but as clinical observers, with the hope of pointing out new lines of research, by which may be increased the knowledge of the regulation of animal heat.

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2. *Sarcomata of the alimentary canal, with the report of a case.*

By E. M. Corner and H. A. T. Fairbank.

We venture to bring before the Society the conclusions we have come to, as a result of a thorough examination of all, or nearly all, the published cases of primary sarcoma of the alimentary tract.

Our attention was called to this subject by operating on a case of sarcoma of the colon with intussusception, which we now record. The list which we have made includes all the cases of sarcoma affecting the canal from the œsophagus to the rectum;[1] sarcomata of the mouth, pharynx, and anus have been omitted. Care was taken in collecting the cases to exclude all those in

[1] Up to the beginning of 1904.

which any doubt existed as to the nature of the growth; and also those in which there was any possibility of the growth in the bowel being secondary to a tumour elsewhere in the body. It has also been our intention to determine some of the points in which sarcomata of the alimentary tract differ from carcinomata of the corresponding regions. Our paper will naturally fall into the following sections: the case to be reported, a summary of the general features of these cases, summaries of the sarcomata of the various regions, their differences from carcinomata, and, finally, the literature. In this way we hope to add many features of etiological and clinical interest to this but little known class.

The case is well worthy of record in itself, as only five examples of intussusception complicating sarcomata of the alimentary canal have been recorded previously, and our case is the only one in which that condition has occurred in the colon, the others involving the small bowel. And, again, it was the eleventh case of sarcoma of the colon.

Case of colic intussusception complicating a sarcoma of the ascending colon.

The following case was briefly reported as an interesting example of colic intussusception in the 'St. Thomas's Hospital Reports,' 1901: [1]

A boy, W. H—, aged 9 years, was admitted to St. Thomas's Hospital on September 5th, 1901. He had been constipated for some time. One month previous to admission he began to have attacks of severe pain in the "stomach," which doubled him up. These attacks lasted for about ten minutes, and took place two or three times daily. A week ago, for the first time, he passed "a good deal of bright blood" with his motions. This happened again shortly afterwards. On the day before his admission to the hospital he became much worse; the pain was very bad, and did not pass away as usual. He vomited a good deal, passed blood and mucus *per rectum*, looking very ill. An abdominal examination revealed a long, sausage-shaped tumour in the left loin and iliac fossa. The right iliac fossa felt "empty." *Per rectum* a mass could be felt, round which the finger could be swept, but no aperture could be felt in it. The tongue was coated with a thin layer of black fur. The urine contained a

[1] Corner, "Pathology of Intussusceptions," 'St. Thomas's Hospital Reports,' 1901.

trace of albumen. The temperature was 97·6°, the pulse 122, the respirations 30. Abdominal section was immediately proceeded with.

Operation.—The abdomen was opened in the middle line below the umbilicus. The intussusception passed so far down the rectum that the apex could not be felt. By gliding the sheath in a downward direction the point was easily brought to the touch. The invagination was easily reduced and found to have started at the middle of the ascending colon, where a rounded tumour about 1½ inches in diameter could be felt within the bowel. The bowel was incised and the sessile neoplasm exposed. The mass was thought to be adenomatous, and was cut away with scissors. The mucous membrane was sutured with fine silk, the incision in the bowel closed in a similar way, and also that in the abdominal wall. The after-history was uneventful, the stitches being removed on the seventh day, the wound having healed by first intention.

In his pathological report, Mr. Shattock described the tumour as a round-celled sarcoma. When discharged from the hospital there was nothing to be felt by palpation of the boy's abdomen.

In nine weeks' time after the operation he was readmitted to the hospital with a tumour, as large as an orange and freely movable, under the right rectus abdominis. There was no trouble with the bowels.

On December 14th the abdomen was again opened through the right rectus and the tumour delivered. It was found to consist of a mass, the size of an orange, with omentum adherent to its anterior surface and the ascending colon on the outer side. Two enlarged glands were felt near the vertebral column. The "recurrence" had taken place rather in the retro-peritoneal tissue than the bowel.

The mass, the involved portion of the ascending colon, and the infected glands were freely excised. The two ends of the bowel were joined together by two rows of silk sutures, circular enterorrhaphy, and the abdominal wall closed *secundem artem.*

Death followed the operation in thirty hours, the boy never recovering from the shock. The *post-mortem* examination was made by Dr. Colman. Every organ was healthy. There were no signs of peritonitis or sepsis. The serous cavities contained some fluid, the result of an infusion. The cause of death was shock.

Microscopical examinations made by Mr. Shattock showed that the tumour was a round-celled sarcoma.

The growth had originated in the submucous tissue of the ascending colon and had developed as a sessile tumour inwards towards the lumen of the bowel. This portion of the neoplasm was removed. Within nine weeks of the "removal" a tumour the size of an orange had appeared on the inner side of the site of the old tumour. And further, the nearest lymphatic glands had been affected. The recurrent tumour and the part of the colon excised are shown to the Society. Towards the lumen of the bowel the tumour is ulcerated, the ulcer communicating with a cavity lined by more or less broken down growth in the interior of the tumour.

General remarks on primary sarcomata of the alimentary tract.

We have collected 175 cases, all of which we believe to be true cases of primary sarcoma of the alimentary tract. Besides these we were unable to consult the records of some twenty others. The cases have been divided up into six groups, according to the portion of bowel affected.

A few remarks will now be made on the occurrence, situation, etc., of sarcomata of the alimentary tract in general, and later, reference in detail will be made to sarcomata of the different portions of the canal.

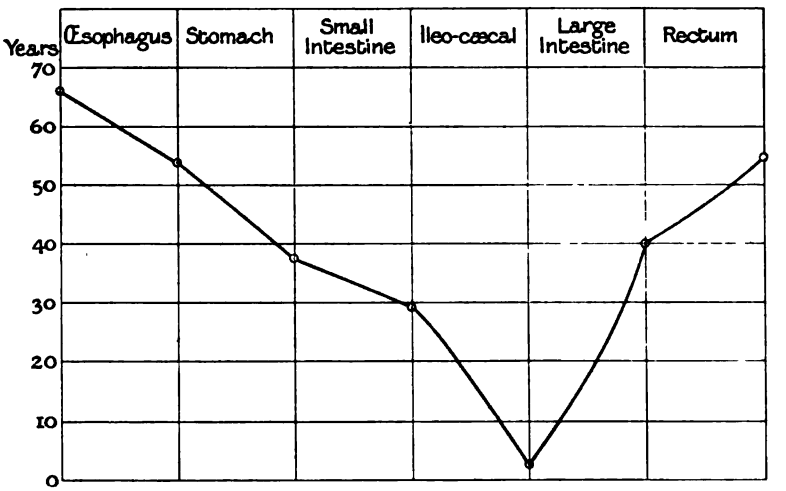
Sex.—Males are more commonly affected than females in the proportion of nearly two to one when all the cases are taken together. The stomach and large intestine are exceptions to this rule; in these portions of the gut the disease occurs in about the same frequency in the two sexes. In the œsophagus the proportion of males to females is as five to one, and in the rectum four to one. Carcinoma affects the intestinal tract of the sexes equally frequently (Ball).

Age.—Sarcoma may occur in any part of the alimentary canal at any age. In the œsophageal and rectal cases sarcoma, like carcinoma, occurs most commonly between the ages of 50 and 70. The stomach is affected most frequently between 40 and 50, and the small intestine between 30 and 40. Of the ileo-cæcal and colonic cases a large proportion occur during the first decade of life. Chart I is designed to show the age at which sarcoma of the various parts most commonly occurs.

Situation.—About 70 per cent. of the cases occurred in the stomach and small intestine. The body of the stomach and the ileum are most commonly the seat of the disease, and appear to be affected with equal frequency. The œsophagus is rather more frequently the seat of sarcoma than is the rectum. The vermiform appendix is very rarely the seat of primary sarcoma. Chart II shows the relative frequency of the disease in the various portions of the bowel.

The pylorus, the colon and the rectum appear to be the

CHART I.



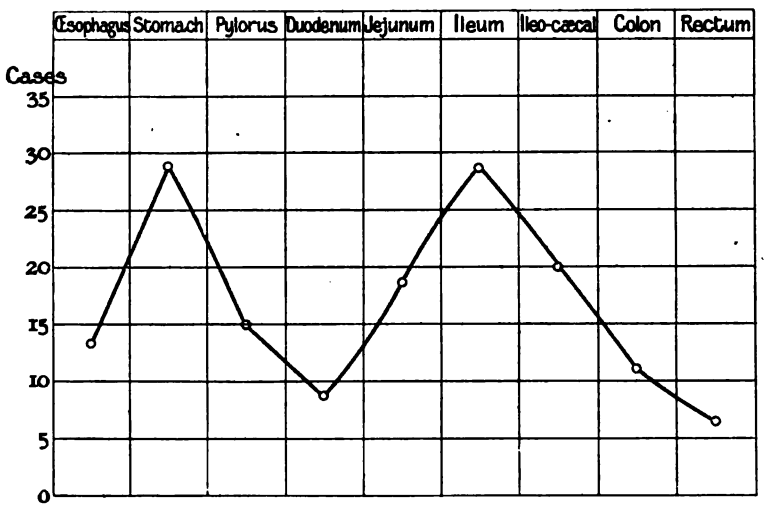
The line indicates the age-incidence of the greatest frequency of sarcoma in the various regions specified.
The above curve does not indicate accurately the frequency of the disease at any particular age, but only denotes roughly the periods of life at which the various parts of the gut are commonly affected.

most common places for a carcinomatous growth. Sarcoma does not seem to show the same predilection for points of friction or irritation which carcinoma does. Although sarcoma, when affecting the œsophagus, occurs usually in the lower third, the cardiac orifice is not the seat of the disease, but a point an inch or two higher up; in this respect it differs from carcinoma. Again, the body of the stomach is more commonly affected than the pylorus. Sarcomata differ from carcinoma in occurring far more frequently in the small intestine than in the large.

Table of regional distribution of alimentary sarcoma.

Œsophagus	14
Stomach	58
Small intestines . . .	65
Ileo-cæcal region . . .	20
Large intestine . . .	11
Rectum	7
	175

CHART II.



The curve indicates the relative frequency of occurrence of sarcomata in the various regions.

Symptoms.—Definite intestinal obstruction occurs in at least 25 per cent. of the cases, but, owing to the brevity of many of the records, this figure is probably too low. Wasting and anæmia, the latter often of a severe type, are usually present.

Pain, of varying degrees of severity, occurs in the majority of cases. The symptoms presented by the disease in the various portions of the bowel will be detailed later. Vomiting occurs more frequently than the number of cases of obstruction would indicate; this symptom was recorded in at least 51 of the

cases; irregular fever occurred in 25 cases. It does not seem to depend in every case on the presence of ulceration of the tumour, though such is often found *post mortem.* Excluding the cases of intussusception, hæmorrhage *per rectum* occurred only nine times; in this respect sarcomata differs very greatly from carcinomata.

In the cases affecting the abdominal portion of the tube, *i. e.* excluding the œsophagus and rectum, we find that a palpable tumour was found in 56 out of 152 cases, *i. e.* in over one third of the total number; many of the tumours were of large size. The blood was examined in too few cases to make the presence or absence of leucocytosis of any diagnostic value. The average duration of life in these cases is about six months.

The following features may serve to distinguish cases of sarcoma from those of carcinoma:

1. The age of the patient.
2. The more rapid course of the disease in sarcoma.
3. The presence of a tumour of considerable dimensions.
4. The early occurrence and the severity of anæmia and wasting.
5. The almost constant presence of pain, often severe.
6. The absence of hæmorrhage.
7. The presence of irregular fever.

Morbid Anatomy and Pathology.—The growth may be annular or may grow as a plaque or polypoid mass projecting into the lumen of the bowel, or the two conditions may be combined.

Excluding the gastric and ileo-cæcal cases, 25 were annular and 19 pedunculated; in the rest the exact condition is not recorded. It has often been stated that sarcoma tends to produce dilatation of the lumen rather than stenosis. This may be true if stenosis is taken to mean an actual shortening of the internal circumference of the tube. But it must be remembered that sarcomata may cause obstruction by the size of the polypoid mass, although the bowel wall may be dilated round the tumour. This condition is particularly well seen in the œsophagus and rectum. It is also probable that obstruction will be caused by interference with the peristalsis of the gut, on account of the infiltration of the muscular wall of the bowel by the growth, although the lumen may be even somewhat dilated.

Dilatation, on the other hand, may occur around a polypoid mass, as a result of the breaking down of masses of growth, or as a true dilatation, the internal circumference of the lumen being increased as the wall becomes infiltrated. Dilatation was recorded in 13 cases, and obstruction from various causes in 44.

The subserous variety, usually found in the stomach, form large pedunculated tumours.

Intussusception occurred 6 times—3 times in the small intestines, twice in the ileo-cæcal region, once in the colon (the case now recorded). Prolapse of the tumour is also commonly seen in the rectum. The growth usually begins in the submucous tissue, although it may begin in the muscular layer or in the subserous tissue. Glandular involvement occurred in as many as one third of the cases, and this although many of the reports are without full details. With regard to metastases, the lungs seem to be remarkably rarely affected; only in nine cases did secondary growths appear in these organs. The liver and the kidneys are most often found to be affected with secondary growths, such as are often seen also in the mesentery and lymphatic spaces.

All varieties of sarcoma are found in the alimentary tract. The round-celled sarcoma is by far the most common type; it occurs in about a third of the cases. The lympho-sarcoma and spindle-celled growths come next in order of frequency. We found three melanotic cases, two in the rectum and one in the ileum.

There are one or two points to which we will now draw attention, as they are of interest in considering the etiology of these tumours. The significance of them we will not venture to estimate, but we think that they may be worth recording.

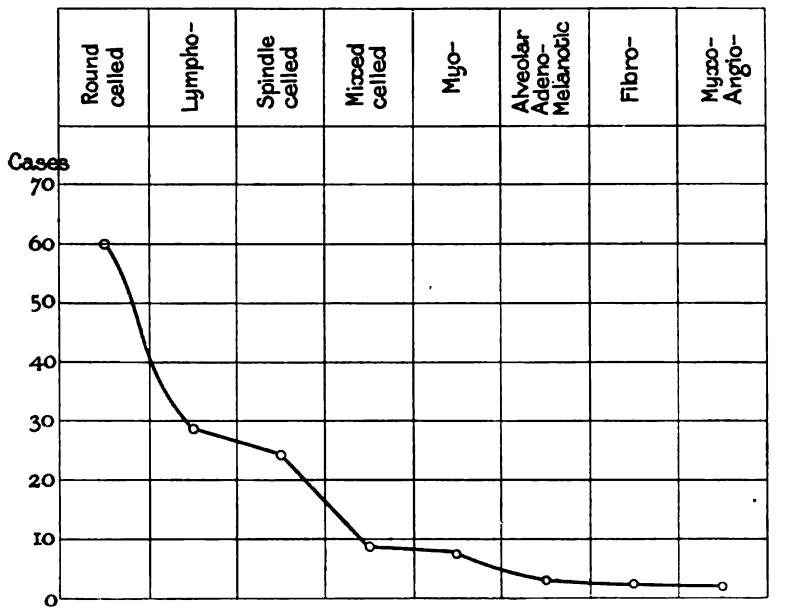
1. Five of the cases of sarcoma of the stomach (57) suffered from gastric symptoms for some years before the onset of severe symptoms. In one case it is hinted that the growth commenced in the scar caused by a bullet wound received some years previously.

2. Two of the cases in which the ileo-cæcal (19) region was affected, not the appendix, had attacks resembling appendicitis for some years previously. In one appendical case a fæcal concretion was present.

3. In three of the seven rectal cases the patients had suffered from hæmorrhoids for some years.

It seems to suggest that as irritation, in its widest sense, is a cause of carcinoma, which is known, so may irritation in the connective tissue be an initial or local factor in the production of sarcomata. Irritation of epithelium leads either to its death or cell-division; irritation of connective tissue produces similar

CHART III.



Showing the relative frequency with which the several varieties of sarcoma have been found. In one case it was not decided from the original microscopic specimens whether the growth was lymphoid tissue or round-celled sarcoma. There has been naturally much confusion in the literature between lymphosarcoma and round-celled sarcoma.

results, *plus* the occurrence of inflammation. In this way young connective tissue is formed, and may be the birth focus of a sarcoma or merely a cicatrix.

Operations.—In all, excision of the growth, with or without resection of the gut, was performed 51 times; 34 recovered from the operation, *i. e.* two thirds. Of these, six are reported as being free from recurrence after periods extending from one

to nine years afterwards. Twelve others are reported as being well from three to eight months after operation.

Sarcoma of œsophagus.

Number of cases collected, 14.

Sex.—More common in males; male, 11 cases; female, 2 cases.

Age.—Most common at same age as carcinoma is, though it may be found at any age. The youngest example was found at 4 years, the oldest at 70 years.

The following table shows the ages of cases:

From 0	to 10	years	1	case.
„ 10	„ 20	„	0	„
„ 20	„ 30	„	1	„
„ 30	„ 40	„	2	cases.
„ 40	„ 50	„	3	„
„ 50	„ 70	„	6	„

Situation.—The most common situation is the lower third of the œsophagus. Of eight cases in which the exact situation is stated, in five the lower third was the seat of the growth, in two the middle, and in one the upper part. Sarcoma differs from carcinoma in not occurring at the cardiac orifice, but a little above this point.

Symptoms.—The symptoms closely resemble those of carcinoma. Gradually increasing dysphagia is almost invariably present. In one case, a patient who died of pneumonia, the growth was discovered *post mortem*, no symptoms of œsophageal trouble having been noticed during life.

Sarcoma differs from carcinoma in running a more rapid course, with great emaciation. Starck says that in sarcoma the pain is much worse, and occurs earlier than in carcinoma. The pain is situated between the shoulders, and is of a severe, stabbing character. It is worse on fasting, especially at night; whereas the pain in carcinoma is worse on eating.

The average duration was six months.

Morbid anatomy and pathology.—The growth commences in the submucous tissue, and usually completely surrounds the œsophagus. In three cases the growth was pedunculated, and formed a long mass, moulded to the shape of a somewhat dilated œsophagus. Ulceration with perforation, and the formation of

gangrenous abscess cavities in the mediastina, lungs, and surrounding tissues, is frequent. Almost every variety of sarcoma has been found. In the recorded cases we find: round-celled, 2; spindle-celled, 3; mixed-celled, 1; lympho-, 1; myo-, 1; alveolar, 2.

Secondary growths were found in 50 per cent. of cases.

In the 14 cases, we find secondary growths occurred in the glands in 7 cases; in liver 2; in bones 2; in bowel 4; in lungs 3; in kidneys 3; in tongue, brain, adrenal, and spleen, 1 each.

Operation.—Gastrostomy was performed in one case. The patient died seven days later from peritonitis and pneumonia. The others were treated medicinally.

Sarcoma of the stomach.

Number of cases collected, 58.

Sex.—The sexes are equally liable to this disease: males, 26; females, 29.

Age.—Affects all ages; between 40 and 50 is the most common period. The oldest case was 78 years of age; the youngest 3½. The following table shows the ages of examples reported:

From	0	to	10	years	2 cases.
„	10	„	20	„	8 „
„	20	„	30	„	5 „
„	30	„	40	„	6 „
„	40	„	50	„	15 „
„	50	„	60	„	8 „
„	60	„	70	„	5 „
„	70	„	80	„	3 „

Situation.—The pylorus is less commonly affected than the body of the stomach. In carcinoma, the pylorus is the seat of the growth in about 60 per cent. of the cases; in sarcoma the corresponding percentage is about 36. Of the instances in which accurate descriptions of the growth were given, we found the pylorus affected in 15 cases, the greater curvature in 6, the lesser curvature in 5, the posterior wall in 10, the anterior wall in 1; the growth was diffuse over the whole stomach in 6.

Symptoms.—Definite obstruction and gastric dilatation oc-

curred in only 4 of the pyloric cases. Dilatation of the stomach without pyloric disease was recorded in 2. The symptoms most commonly noted were pain, vomiting, and wasting. Hæmatemesis only occurred in three cases, a point which helps to distinguish these cases from carcinoma. A palpable tumour (in several cases of enormous size) was found in 22 cases, and possibly occurred in others in which the notes are short and imperfect. Irregular pyrexia was noted in 4 instances. Leucocytosis was found in 5 cases, and was stated to be absent in 6 others in which the blood was examined. It does not seem to depend on ulceration or sloughing of the growth, and does not appear to be of any diagnostic value. Anæmia is a noticeable feature, and occurs early in the course of the disease. In 4 cases the anæmia was stated to be extreme, and in 1 the diagnosis of "pernicious anæmia" was made.

Jaundice was present in 4 cases, ascites in 11, œdema of legs in 5. One case was diagnosed as a left movable kidney, another was an ovarian cyst; the first was a pedunculated subserous growth, and the second was a myosarcoma undergoing cystic degeneration, and was, presumably, of large size.

Dr. Soltau Fenwick says "a large omental tumour and a large nodular liver" are much more in favour of carcinoma than sarcoma. He also draws attention to the occurrence of congestion and hyperplasia of the spleen (15 per cent. of cases), and of nodules in the skin about the umbilicus, both of which he considers of value in cases of sarcoma.

Several examples had a history of dyspepsia of two, three, or even twenty years' standing. One case had a history of an old bullet wound of the stomach.

The following points might help in the differentiation from carcinoma: the rapid course, with marked anæmia, the absence of hæmatemesis or gastric dilatation, the presence of a large tumour, and, possibly, the age of the patient.

Morbid Anatomy and Pathology.—The growth most commonly is submucous, the mucous membrane remaining intact for a considerable time. The growth may commence in the muscular or in the subserous tissue; in the latter case it forms a pedunculated tumour outside the stomach. A number of very large examples of these tumours have been reported. The mass may project into the cavity of the stomach and ulcerate, or it may

spread widely in the stomach-wall and cause little or no ulceration. It may surround the pylorus and cause obstruction, or may form a constriction near the centre of the stomach (hour-glass stomach). The large tumours, especially of the subserous variety, are liable to undergo cystic degeneration. In one the large cavity thus formed was opened at the operation.

The average duration of symptoms before death in the cases not operated upon was about nine months. Dock states that in nine cases he found free hydrochloric acid absent from the gastric juice, and that in most of these lactic acid was present. The same observer states that anæmia and leucocytosis are usually present.

All varieties of sarcoma have been found. We found round-celled, 21 cases; spindle, 7; lympho-, 8; mixed-celled, 4; myo- 6; fibro- and alveolar, each 2, and myxo- and angio-, each 1.

Secondary growth may occur in at least 40 per cent. of cases, and probably in more. The glands in the neighbourhood of the stomach are commonly affected; the liver, the kidneys, other portions of bowel, and the omentum are the other situations in which secondary growths are commonly found, in the order of their frequency.

Operation.—Excision of the growth were performed in 15 cases, 12 of which recovered from the operation. Four are reported as being alive and well after 4, 5, 12, and 24 months respectively since operation.

One case died of recurrence after eight months. The average duration of symptoms before operation in six successful excisions was ten months. Gastro-enterostomy was performed in one case, which died of shock. Three cases were subjected to exploratory laparotomy, and in one of these a large cavity in the growth was opened.

Sarcoma of small intestine.

Number of cases collected, 65.

Sex.—The proportion of males to females is about three to one. Males 44, females 16.

Age.—It occurs earlier in life than carcinoma, though the disease has been found at almost any age. More than half the

cases were between 20 and 40 years of age. The oldest was 70 the youngest was "new born!" We found:

From	0	to	10	years	7 cases.
„	10	„	20	„	7 „
„	20	„	30	„	16 „
„	30	„	40	„	19 „
„	40	„	50	„	10 „
„	50	„	70	„	4 „

Situation.—The liability of sarcoma increases as one passes downwards, the ileum being by far the most common seat of the growth. We found the duodenum affected in 8 cases, the jejunum in 19, and the ileum in 28. In 9 the exact seat was not stated.

Symptoms.—The usual symptoms are pain, wasting, anæmia, vomiting, with constipation or diarrhœa. Vomiting is stated to have occurred in only 15 cases, but it was probably present in many more. Constipation, apart from definite obstruction, was present in 8, diarrhœa was recorded in 10, and the passage of pus and blood *per rectum* in 2, in neither of which was there an intussusception. A tumour was felt in the abdomen in 18 cases. Definite obstruction, recognised clinically, occurred in 12 cases, and in some of these the symptoms were acute, without any previous signs of chronic obstruction. Intussusception was found in 3 cases, all of which died without operation. Irregular fever occurred in 10 cases, and was stated to be absent in 5. Leucocytosis was found in 5 cases, in all of which either ulceration of the bowel or peritonitis was present.

The diagnosis would seem to be extremely difficult; the only point which might assist in differentiating a case of sarcoma from one of carcinoma would be the age of the patient. Diagnosis from other diseases, such as tubercular peritonitis and chronic intussusception, prior to operation, must be usually impossible.

The average duration of symptoms in cases not operated upon was about five months.

Morbid anatomy and pathology.—The growth varies from a single polypoid mass to an extensive tubular infiltration of the wall of the bowel, with several plaques in the bowel above and below the main mass. Obstruction, apart from intussusception, may be caused in two ways: first, by definite narrowing or constriction of the tube; this was noted *post mortem* in 4

cases; secondly, by the formation of large masses projecting into the bowel, the bowel itself being really dilated. This occurred in 8 cases at least, making up the 12 in which definite symptoms of obstruction occurred.

Dilatation of the tube was noted *post mortem* in 9 cases. This may occur as an actual dilatation of the tube as the wall becomes more or less uniformly infiltrated, or may result from the ulceration and sloughing of large polypoid masses which had projected into the lumen of the bowel.

The growth usually commences in the submucous tissue, and is most commonly of the round-celled variety. A unique case of melanotic sarcoma is reported by Sir Frederick Treves. We found the round-celled variety 21 times, lympho-sarcoma 14, spindle-celled sarcoma 7, myosarcoma 2, melanotic 1.

Secondary growths were found in about 30 per cent. of cases. Involvement of the nearest glands took place in nearly half the cases. Masses of growth in the mesentery, apart from glands, are commonly found. The liver, kidney, and other parts of the bowel are the most frequent situations for metastases.

Operation.—Resection was performed in 18 cases, of which 11 recovered from the operation. Of these 11, 2 were alive and well one year later, 1 was alive and well eight years later. Three died of recurrence or metastasis after three, seven, and eight weeks respectively.

Exploratory laparotomy was performed in 6 cases, in 1 of which enterostomy was performed.

Sarcoma of the Ileo-cæcal Region.

Number of cases collected, 20.

Sex.—Males seem more liable to the disease than females: males, 12 cases; females, 8.

Age.—In two thirds of the cases the patients were under 30 years—*i.e.* much earlier than carcinoma. The oldest was 66 years, the youngest 2 years. We found:

From	0	to	10	years	7 cases.
„	10	„	20	„	1 case.
„	20	„	30	„	5 cases.
„	30	„	40	„	2 „
„	40	„	50	„	1 case.
„	50	„	70	„	3 cases.

Situation.—The cæcum was affected in 7 cases, the ileo-cæcal valve in 1, and the appendix in 4. A fifth case of primary sarcoma of the appendix is reported by Glazebrook, but we were unable to consult the report of the case. In the remaining 7 cases the exact origin of the growth was doubtful.

Symptoms.—The symptoms are often similar to those of appendicitis, for which the disease has usually been mistaken. The symptoms may be those of acute or recurrent subacute appendicitis. Pain, vomiting, constipation, and the formation of a tumour in the right iliac region are the usual points of the case. Definite intestinal obstruction occurred in 4 cases, in 2 of which an intussusception was present. A palpable tumour was present in 11 cases, being movable in 3, and fixed in the rest. In 1 the diagnosis of movable left kidney was suggested. Fever was present in 9 cases. In 2 there was a history of appendix trouble of long standing.

The duration of symptoms in 6 cases in which excision was not performed averaged five months.

Morbid anatomy and pathology.—We have little information on this subject. Coils of bowel have been found matted around the cæcum, as in appendicitis. In one case an annular growth at the ileo-cæcal valve, more marked on one side, was associated with a partial intussusception of ileum into the colon. A little above the valve was a secondary nodule in the mesentery and attached to the ileum. It would seem that this mass passed through the valve with the attached ileum, but the account is not quite clear. In two cases a cavity had formed, communicating with one or two coils of bowel. Both cavities were opened as appendix abscesses and drained. In one case the appendix, which was the seat of the primary growth, was greatly dilated. In another appendix case there was present a fæcal concretion. In yet another in which the appendix was the seat of the disease, the wall of the cæcum was infiltrated for a quarter of an inch round the orifice of the appendix.

Round-celled growth is again the commonest; it was found in 9 cases. In 4 the growth was a lympho-sarcoma, and the spindle-celled, mixed-celled, and "adeno" varieties were each found once.

The mesenteric glands were diseased in at least 5 cases, and the retro-peritoneal or cervical glands in 3.

Metastases were found in the lungs, spleen, liver (2), kidney, and stomach.

Confusion has arisen in one or two cases where granulation tissue has been mistaken to be sarcomatous.

Operation.—Resection of the growth and bowel was performed in 11 cases, with 7 recoveries. The duration of symptoms before operation averaged five months. All the successful cases of resection are reported as being alive and well for periods varying from three to eight months after operation.

In 5 cases exploratory laparotomy was performed, in 2 of which gangrenous abscess cavities were opened and drained.

Sarcoma of Large Intestine.

Number of cases collected, 11.

Sex.—Males and females seem to be equally liable to the disease in this region—males, 3; females, 4.

Age.—Of 6 cases in which the age was stated, 3 occurred in children under 10, and 1 in each of the three succeeding decades. The oldest was 38, the youngest 4 years.

Situation.—The growth may affect any portion of the gut. The ascending colon was affected in 3 cases, the transverse in 1, the splenic flexure in 2, the ascending colon in 1, and the sigmoid in 2.

Symptoms.—The symptoms appear to be those of chronic obstruction, even though definite constriction be absent. In 5 cases intestinal obstruction supervened, 1 being the case now reported in which an intussusception was present. In 1 other case there was entire absence of symptoms until the onset of acute obstruction. A tumour was felt in 6 cases; in 1 the mass measured 19½ inches in circumference. Pyrexia occurred in 2 cases.

Morbid anatomy and pathology.—Polypoid or discoid masses and annular growths occurred in an equal number of cases. Dilatation of the lumen of the bowel was noticed in 2 cases, in 1 of which there was an "aneurismal" dilatation of the bowel capable of holding a pint of fluid. In 2 cases obstruction was due to stenosis of the bowel.

The round-celled is again the most common variety, and was found in 7 cases. In 2 it was spindle-celled, in one mixed-

celled. Metastases were found in 6 cases. In one instance the whole abdomen was involved by secondary nodules. Glandular infiltration was noted in 3. The lungs (four times), the ovaries (twice), the spleen (twice), and the kidneys, liver, pancreas, bowel, and brain (each once) were the seats of the metastases.

Operation.—Excision was performed in 2 cases. Both died of shock.

Sarcoma of the Rectum.

Number of cases collected, 7. (The notes of 4 other cases could not be consulted.)

Sex.—Males would seem to be more commonly affected: Males, 4 cases; females, 1 case.

Age.—The ages of only 5 cases could be obtained, and were found to lie between 43 and 63, at which time carcinoma is most commonly found.

Situation.—Those occurring at the anus have been excluded. All the rest were within reach of the examining finger.

Symptoms.—The symptoms usually commence with constipation and pain in the rectum, the latter being increased by defæcation. Some hæmorrhage may take place after the passage of a motion. In some instances such symptoms as the above, associated with hæmorrhoids, had existed for periods varying from one to twenty years. Later, a mass prolapses whenever the bowels are opened. At first it is reducible, but later may remain permanently outside the sphincters, subsequently increasing greatly in size. In one case the mass, which twelve months before had been the size of a walnut, at the time of the operation had increased to the size of a fœtal head. The tumour was excised, and recovery followed. Intestinal obstruction without any prolapse occurred in 2 cases, prolapse alone in 5. Distinct wasting and pruritus ani were each noted once. The occurrence of diarrhœa, so often seen in carcinoma, was not recorded.

Morbid Anatomy and Pathology.—The growth was polypoid in 6 cases. In 1, figured in Treves' 'System of Surgery,' there was an annular growth extending for five inches. The submucous tissue is the seat of the growth. In 1 case cystic degenera-

tion was found. The tumour was of the spindle-celled variety in 3 cases, lympho-sarcomatous in 1, melanotic in 2, alveolar in 1. In one of the melanotic cases, three separate polypi were found, two of which were pigmented. In the other case the veins were found invaded, and the blood contained pigmented cells larger than leucocytes. In one (spindle-celled) case there was a secondary nodule in the skin of the thigh. It would seem that involvement of glands, and the formation of secondary growths were less common than is the case in carcinoma of the rectum.

It must be remembered that it is impossible to estimate the duration of the growth.

Operation.—Excision of the mass was performed in 5 cases, with 3 recoveries. Two died of peritonitis. One case (melanotic, with three separate masses) was alive and well nine years later (Ball).

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May 17th, 1904.

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3. *Two cases of emphysematous gangrene due to the* Bacillus aerogenes capsulatus.

By L. S. Dudgeon and P. W. G. Sargent.

Case 1.—S. A—, a charwoman aged 37 years, was admitted to St. Thomas's Hospital on September 8th, 1904, under the care of Mr. Battle. She had been knocked down in the street by a cart, and the right forearm had been crushed by the horse's hoof. When admitted, within half an hour of the accident, there was a compound fracture of the ulna between the lower and middle thirds. A contused lacerated wound, through which projected bruised and torn muscle, extended from the base of the thumb to the olecranon. There was much ecchymosis and the hand was somewhat swollen.

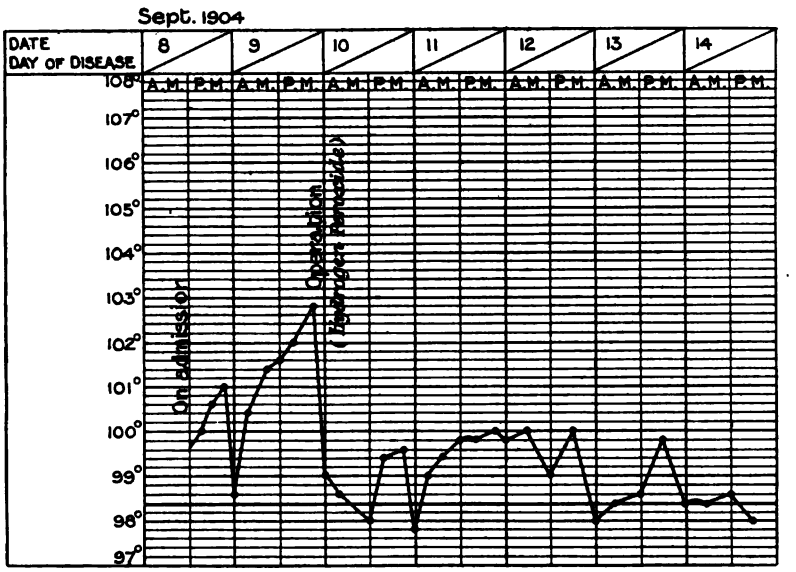
The limb was carefully cleansed and the wound partially sutured. In the following morning the hand was more swollen, and the patient complained much of pain. She looked flushed and was rather restless. There was no sugar or albumen in the urine. The temperature, which had risen to 100·4° in the morning, reached 102·8° on the evening of the second day, forty hours after the accident. The pulse was now 110 and the patient quiet and apathetic, with dry tongue and flushed cheeks. There was no vomiting. The dressings were taken down, when the following condition was found:

An enormous quantity of thin yellow fluid with a peculiarly disgusting smell soaked the dressing. Around the margin of the wound, on the dorsum of the forearm, was a purple red area of skin about two inches wide; over the rest of the forearm appeared a dull, coppery-red mottling. A red blush extended above the elbow for a distance of three inches in its whole

circumference, and on the inner side extended in a tongue-shaped process as high as the axilla. Subcutaneous gas crepitation could be felt over the whole forearm from wrist to elbow, but not above this level. Marked œdema involved the whole limb, gradually diminishing in degree from the elbow upwards.

Amputation was at once proceeded with. No tourniquet was

CHART I.



used nor were any chemical solutions employed during the operation. The limb was removed at the junction of the upper and middle thirds by the method of skin flaps and circular division of muscles. The incisions passed through the red œdematous area on the inner side, from which cultures were taken immediately after section. After tying off all bleeding points, and washing the surface of the stump with sterile saline solution, the flaps were turned back, with their raw surface outwards, and covered with sterile gauze soaked with peroxide of hydrogen of ten-volume strength. For the next twenty-four hours this dressing was kept constantly wet by pouring upon it the same solution of peroxide of hydrogen. A few days later the flaps were turned down and loosely sutured, and healing rapidly ensued.

After the amputation the temperature never rose above 100°, and the symptoms of toxæmia rapidly passed off. At no time was any sugar or albumen present in the urine.

Bacteriological examination.—Culture-tubes of glucose formate broth, sodium sulphindigotate glucose broth, and ordinary broth were inoculated from the area of emphysema, and cover-slip preparations were also made from the thin blood-stained fluid, which, together with a large quantity of gas, was escaping from the wound. The cover-slips were stained by Gram's method and counter-stained with weak carbol-fuchsin. Large straight bacilli, mostly with somewhat rounded ends, were present in enormous numbers. They stained well by Gram's method. Some of the bacilli, however, especially the longest forms, stained unevenly; *i.e.* the bacilli stained only faintly by Gram's method, whilst all along their margins, coarse, deeply-staining granules were visible. The micro-photograph of one of the film preparations shows this point. A few scattered cocci, arranged singly or in groups, also staining by Gram's method, were present in the films. No other bacilli were seen. The culture-tubes of Kitasato and Weil, as well as the broth tube, were incubated at 37° C. The first two tubes were incubated anaerobically in modified Buchner's tubes. A pure growth of a coccus was obtained from the aerobic broth tube which stained by Gram's method, but from the anaerobic tubes both cocci and bacilli, the latter identical with the organism seen in films from the tissues, were obtained. The bacilli grown artificially, however, did not show the granular markings which were so well seen in those obtained direct from the tissues. The anaerobic tubes were plated in a series of three dilutions on glucose agar plates, which were then placed in Bulloch's anaerobic jar and incubated for three days. Two varieties of colonies were obtained: (1) orange-coloured granular colonies, which were composed of Gram-staining cocci arranged as staphylococci, and similar to the cocci obtained by the aerobic method; and (2) pale granular colonies which microscopically resembled fern-leaves radiating outwards and meeting together at a common centre. These colonies appeared to grow best in the depth of the sugar agar. Near the centre of each colony gas formation had occurred. Film preparations from two of these colonies showed a Gram-staining bacillus similar to that previously

described. Sub-cultures of the coccus were made on various artificial media, and it was found to be the *Staphylococcus pyogenes aureus*. Sub-cultures of the bacillus were made in glucose broth and grown anaerobically. Only a slight turbidity occurred, even after several days' incubation, and sub-cultures proved to be sterile. One c.c. of a glucose broth culture of the bacillus was inoculated into the subcutaneous tissues of two guinea-pigs, but the experiment unfortunately only served to show that the organism had died out.

At the time of the amputation both aerobic and anaerobic culture-tubes were inoculated from the raw surface of the flaps, and both proved to be sterile.

Portions of the muscle from the emphysematous area were fixed in alcohol and embedded in paraffin. Sections were stained by Gram's method and counter-stained with saffranin. Enormous numbers of Gram-staining bacilli morphologically identical with those depicted in the microphotograph were found to be present.

There appears to be little doubt that the bacillus present in large numbers in the emphysematous tissues was the *B. aerogenes capsulatus* of Professor Welch. We greatly regret that it should have died out in spite of every precaution.

Two points of special interest to be observed are: (1) that the granular marking indicating a peculiar variety of capsule which was present in so many of the bacilli obtained direct from the tissues was absent from those grown artificially. We cannot recall a similar observation before, even in the classical description of the morphology of the bacillus which has been given by Professor Welch and Professor Fraenkel; (2) the colon bacillus was not present in the tissues in this case, an observation which is important in view of the opinions of Professor Welch referred to above.

CASE 2.—D. R., a boy aged 12 years, was knocked down and run over by a tram-car, the wheel of which passed over his right leg. When admitted to St. Thomas's Hospital, shortly after the accident, the following condition was found: There was a transverse comminuted fracture of the tibia at about its middle. Just above this level was a clean vertical wound reaching down to the periosteum, and on the posterior aspect of the limb at the same level was a transverse contused wound

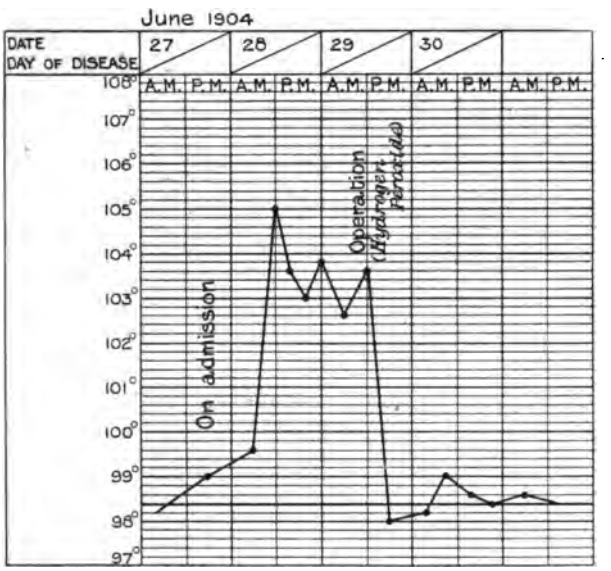
through which projected a mass of lacerated muscle, whilst below this was another smaller wound, the two being separated by an undermined bridge of skin a couple of inches in width. The leg below presented a natural appearance, and both the tibial arteries could be felt pulsating. The temperature was 98°, the urine was normal, and there were no signs of visceral disease. The wounds were thoroughly cleansed with ether-soap and water, followed by peroxide of hydrogen, and partially sutured, a gauze drain being left in.

Twelve hours later the temperature rose to 105°, the pulse was 120, and the boy looked very ill, but, except for some œdema, the leg looked healthy. The temperature kept up all that day between 103° and 104°, and the general constitutional disturbance became more marked. Thirty-six hours after the accident the wound was again examined. The bridge of skin mentioned above was now of a dull green colour, and round the posterior wounds was a red blush over a very limited area. Gas crepitation could be felt in this area, and extending as high as the tibial tubercle. The removal of some stitches was followed by the escape of clear yellow fluid and gas bubbles in considerable quantity. From this fluid cultures were taken, and coverslip preparations were made. The whole leg was now pale and tensely œdematous, but gas crepitation scarcely extended below the wound at all. The boy was now very ill, with a pulse of 160, temperature 104°, dry brown tongue, and active delirium. Operation was undertaken forty-one hours after the accident. The area of gas crepitation had now extended to the level of the patella, the redness following in its wake. No glandular enlargement was detected. The limb was amputated by the circular method in the upper third of the thigh, the abdominal aorta being digitally compressed in order to avoid damage to the tissues by the use of a tourniquet. Hæmorrhage having been arrested, the wound was left unsutured, and covered with a gauze dressing soaked in peroxide of hydrogen of ten-volume strength. For the next twelve hours the dressing was kept constantly wet with the same solution, in order to insure a constant supply of nascent oxygen in case any stray bacilli, so readily killed by oxygen, should be present on the surface of the wound.

The subsequent progress was remarkable only for the rapid

return to health, of which the temperature chart gives a somewhat graphic indication. The stump for two or three days showed very little sign of reaction, but when once the healing process began it was rapid and uneventful. This delay may be attributed either to the intense toxæmia or to the action of the peroxide of hydrogen. At no time was any sugar or albumen detected in the urine.

CHART II.



Bacteriological examination. — Cover-slip preparations were made from the emphysematous tissues and from the flaps after amputation of the patient's leg. A broth tube and a glucose indigo carmine broth tube were inoculated from the emphysematous tissues and also from the flaps. The glucose broth tubes were put into modified Buchner's tubes and incubated anaerobically at 37° C.

Examination of the cover-slip preparations. — These were stained by Gram's method and counter-stained with weak carbol fuchsin. Leishman's blood stain was used for the demonstration of capsules. Large numbers of bacilli with square ends, which stained deeply by Gram's method, were present in the films. Bacilli with rounded ends, short and plump, and which did not

stain with Gram, and groups of cocci which did stain with Gram were also present in large numbers. No true capsules were seen.

Examination of the original culture-tubes.—The anaerobic broth tubes were examined after seventy-two hours' growth at 37° C. There was an abundant growth in the broth-tube which had been inoculated from the gaseous tissues, and the blue coloration had been completely removed. There was a less abundant growth in the other tubes which had been inoculated from the flaps and in the aerobic culture tube from the gaseous tissues. Cover-slip preparations were made from the indigo carmine tubes and similar organisms were present to those which were found in the films made from the patient's tissues. In the films which were made from the aerobic tubes only non-Gram-staining bacilli and Gram-staining cocci were present, while in those made from the flaps only cocci were present.

Method of isolation of the various organisms and their cultural characters.—The tube from which the anaerobic bacilli were found was plated in glucose agar, and the plates were incubated in Bulloch's anaerobic jar in the hot oven. The other tubes were plated aerobically in ordinary agar.

Examination of the glucose media after seventy-two hours' incubation showed large numbers of greyish colonies with a central dark spot. If viewed with a microscope, granular colonies with a faint and slightly irregular edge were observed, and also a few colonies which resembled fern-leaves. Two other types of colonies were present: (1) large, moist, dirty-white coloured colonies with a regular margin, and (2) small, pure white, and regular colonies. Gram-staining bacilli were present in film preparations from the first type of colonies, non-Gram-staining bacilli from the second type, and lastly, Gram-staining cocci from the last mentioned colonies.

Sub-cultures were now made from the various colonies on to various artificial media.

A pure culture of a *Staphylococcus albus* was obtained from all the original tubes, and in pure culture from the flaps. There was nothing abnormal as regards the morphological and cultural characters of the organism. Gelatin media were liquefied in four days.

Non-Gram-staining bacillus.—This bacillus formed an abundant growth in broth, in twenty-four hours, with some gas production.

Subcultures were made on various artificial media and incubated either at 37° C. or 22° C.

Agar.—Thick, dirty white, and moist growth, with an irregular spreading edge along the track of the needle.

Litmus milk.—This was acidified in twenty-four hours, and a solid clot formed in forty-eight hours, which was not redissolved after many days' incubation.

Potato.—Thick, moist, yellowish-white, and abundant growth in forty-eight hours.

Glucose jelly.—Extensive gas production in twenty-four hours, but no liquefaction of the medium after fourteen days' incubation.

Neutral red jelly.—Good growth along the track of the needle within twenty-four hours. The medium was slightly decolourised in forty-eight hours. At the end of four days' incubation at 22° C. the jelly tube in its upper portion had become a golden-brown colour.

Peptone water.—Slight indol production after six days' incubation. The bacillus grew well in glucose broth under anaerobic conditions. The bacillus was found to be non-motile whether it was grown on glycerine agar or in liquid media.

Pathogenicity.—One cubic centimetre of a twenty-four-hour broth culture was injected subcutaneously into a guinea-pig's leg. The animal was very ill for twenty-four hours. There was an extensive swelling at the seat of inoculation, but there was no gas-production. The swelling subsided in the course of a week without any evidence of suppuration. This bacillus may therefore be classified as a member of the *Bacillus coli* family.

Gram-staining bacillus.—This bacillus grew well in glucose broth, and after several days' incubation at 37° C. a viscid deposit could be seen in the culture-tube. Subcultures were made in the following media and incubated at 37° C. in Bulloch's anaerobic jar. The jelly media were incubated in modified Buchner's tubes at 22° C.

Agar.—Small colonies appeared in twenty-four hours, but at the end of forty-eight hours' incubation large, moist, and viscid isolated colonies had formed along the line of the needle.

Litmus milk.—At the end of twenty-four hours the medium was acidified.

At the end of forty-eight hours the casein and also globules of

fat were floating on the surface of the turbid whey. The casein was also adherent to the sides of the tube. Large gas bubbles could be seen on the surface of the liquid.

Another litmus milk tube was inoculated with the organism in question, and then heated up to and at 80° C., for ten minutes. The culture-tube was then incubated anaerobically at 37° C. No growth was obtained after several days' incubation.

Glucose agar shake.—Good gas production occurred at the end of seventy-two hours.

Glucose jelly shake.—The result was similar to what had been obtained in the case of glucose agar. The medium was not liquefied after several weeks' incubation.

Spore-formation.—The bacilli were stained for spores, but with a negative result. The bacillus was found to be non-motile.

Pathogenicity.—One cubic centimetre was inoculated subcutaneously into a guinea-pig's leg. An extensive gas-containing cavity had formed at the end of four hours, and at the end of twenty-four hours the pig was moribund.

A very extensive bloody emphysematous œdema was present, which extended from the seat of inoculation all over the animal's body and caused the skin to be separated from the deeper structures. There was a large amount of blood-stained turbid fluid present throughout the affected regions. Enormous numbers of large bacilli which retained Gram's stain were present, and a pure culture was obtained of a bacillus similar to the above.

Inoculation of a rabbit.—Two cubic centimetres of a broth culture of the bacillus isolated from the patient's tissues were inoculated into the vein of a rabbit's ear. The animal was killed at the end of two minutes, and the body incubated at 22° C. for twenty-four hours.

Result.—The animal was found to be about twice the original size. There was emphysema of the subcutaneous tissues and a large quantity of free gas in the peritoneal cavity. The animal's eyes were protruding from its head. There was gas in the blood-vessels throughout the body. All the viscera were foaming, but this was especially obvious in the case of the liver, spleen, and kidneys. The peri-renal fat was blown up into a kind of air-bag.

Sections of the liver were fixed in alcohol, cut in paraffin, and stained with Leishman's stain; and also by Gram's method.

Enormous masses of bacilli were present in the blood-vessels, and between the separated liver cells, and in the connective tissue. The liver cells were blown apart by the gas formation in the animal's tissues. The bacillus stained well by Gram's method.

No capsule could be identified around the bacillus in the

FIG. 1.

A microscopic section of "foaming liver" from a rabbit, inoculated intravenously with 2 c.c. of a culture of *B. aerogenes capsulatus*, showing large numbers of the bacillus. The liver-cells are separated by wide spaces due to the formation of gas in the tissues. $\frac{1}{12}$th oil immersion.

animal's tissues. The organism may, therefore, be described as the *Bacillus aerogenes capsulatus* of Welch and Nuttall.

It will be noticed that the *Bacillus aerogenes capsulatus* isolated in this case of emphysematous gangrene did not liquefy gelatine as it is usually stated to do. This, however, has been our experience of the organism, as we have not found that it has caused liquefaction of jelly in any case in which we have isolated it. Veillon and Zuber described this bacillus under the name of the *Bacillus perfringens*, and they positively state that it does not liquefy gelatine. They refer to this fact as the only distinction between their bacillus and Fraenkel's.

The results which we obtained from the inoculation of litmus milk closely resembled the cultural characteristics of the *Bacillus enteritidis sporogenes*, but the *Bacillus aerogenes capsulatus* does not produce the change in the litmus milk after heating to 80° C., which phenomenon occurs in the case of the *Bacillus enteritidis*. The pathogenic properties of the two organisms are also entirely different.

We may say that there is no evidence that the cultures of the *Bacillus aerogenes capsulatus* which we have obtained in this case have produced spores.

In conclusion, this case may be described as one of emphysematous gangrene, from which have been isolated the following micro-organisms :—

(1) The *Bacillus aerogenes capsulatus;*
(2) The *Bacillus coli;*
(3) *Staphylococcus albus.*

Remarks.—Besides these two cases we have also had the opportunity of examining two others of traumatic gangrene with subcutaneous gas production, in which, however, no specific micro-organism was isolated. One was an old man whose leg had been crushed by a tramcar. When admitted there was a compound fracture of the tibia, with much damage to the soft parts, but the tibial vessels were uninjured. The urine was normal. Suppuration occurred, and the toxæmic symptoms were rather severe. On the third day subcutaneous gas-crepitation was noted, and amputation carried out. The patient did not rally from the operation. Coverslip preparations and cultures were taken at the operation, as in the other cases. The coverslips showed only Gram-staining cocci and no bacilli. Cultures, both aerobic and anaerobic, gave a pure growth of *Staphylococcus pyogenes aureus*. The second case of this class was that of a boy, aged 15 years, whose thighs had been run over by a heavy cart. The right limb had to be amputated for gangrene due to rupture of the femoral artery. There was a compound fracture of the left femur in its lower third, which suppurated. It was not until the sixth day that there was any marked œdema. On the eighth day there was discoloration round the wound, and the cuticle peeled off easily. There was a peculiar musty smell. Incisions were made, giving exit to a quantity of blood-stained fluid, but no definite pus. On the

twelfth day subcutaneous gas-crepitation was noted. The general condition was one of intense toxæmia. The urine was normal throughout. Amputation was performed on the twelfth day, and the patient recovered. Film preparations from the tissues in the emphysematous area showed only bacilli which did not stain by Gram. Anaerobic and aerobic cultures yielded growths of the *B. pyocyaneus* only.

In comparing these two cases in which we regard the gas as only a decomposition product with those in which the *B. aerogenes capsulatus* was found, we note the following principal points of difference. In the *B. aerogenes* cases the incubation period was much shorter, being only 36 and 40 hours respectively, the toxæmic symptoms were more severe, whilst the amount of peculiar yellow offensive fluid exuded was literally enormous. But in making a diagnosis we attach the greatest importance to the examination of film preparations. In both the *B. aerogenes* cases large numbers of Gram-staining bacilli were present in the films, whilst in the others no organisms resembling Welch's bacillus were seen. In the treatment it occurred to us that the free use of peroxide of hydrogen on the unsutured stump would be a rational measure directed against an obligatory anaerobic bacillus.

November 15th, 1904.

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4. *Two methods of comparing normal with abnormal tissues beneath the microscope.*

By S. G. Shattock and C. F. Selous.

It is more particularly in the study of pathological conditions of the bone marrow and central nervous system that a comparison with the normal is at times a great desideratum. An estimation of the proportion of the different cells constitutes, in fact, an important element in the study of bone marrow, and the same is true in the case of diseases of the central nervous system which involve an atrophy and disappearance of nerve-cells.

The study of two slides, normal and abnormal, in succession under the same microscope involves the lapse of an interval which is hazardous to the retention of the mental images upon which the comparison depends; the use of two microscopes presents similar disadvantages.

The two methods we venture to bring under notice we designate as that of superposition, and the use of a composite block, and, although more particularly adapted for class teaching, they may be at times useful in other ways.

Superposition.—This consists in the mounting of a normal section underneath the diseased, so that by merely altering the focus the two may be studied in rapid succession, and thus readily compared.

The sections must be cut from paraffin blocks and should be not more than 2 μ in thickness. No adhesive is necessary for the fixation of the sections to the glass.

The particular technique adopted in the case of the specimens exhibited at the meeting was as follows: The sections are received from the razor of the microtome and transferred to the surface of hot water in a capacious glass dish. From the hot water a selected section is transferred to a slide which has been cleaned with alcohol and afterwards rubbed by means of the finger with hot water in order to remove the polish, the transference being made by placing the slide in the water beneath the section selected. The section having been arranged in position, the excess of water is drained off and the section pressed upon the slide by laying over it a strip of smooth paper which has been dipped in alcohol, and passing the finger in one direction three or four times over the paper, which is then slowly raised from one side and removed. The slide is finally placed on blotting-paper on the top of the paraffin oven, covered with a glass frame to exclude dust, and allowed to dry.

A second section (cut from the second of the two blocks) is similarly dealt with, but is received on a thin (No. 1) cover-glass in place of the slide. The sections so fixed are next treated, separately, in the usual manner with xylol and absolute alcohol, and stained.

After staining, the usual dehydration with absolute alcohol and clearing with xylol are carried out, the cover-glass being

finally mounted with xylol balsam in such a way that the section on its lower side lies directly superposed upon the section on the slide.

It will be found that both the sections can be readily studied beneath a $\frac{1}{12}$ oil immersion, which will penetrate through the upper without detriment to the definition of the lower, and with little reduction of light.

Although the sections are mounted in direct apposition there is a distinct microscopic interval between them due to the intervention of a thin layer of the mounting medium.

Even if a cover-glass is placed over the section on the slide, and the second cover-glass (to the lower side of which the second section is fixed) is mounted over the upper surface of the first, a Leitz $\frac{1}{12}$ will penetrate through the uppermost cover, the upper section, and the lower cover-glass to the lower of the two sections.

But since, as already noticed, there is a distinct microscopic interval between the sections when mounted in direct apposition, the use of the intervening cover-glass is unnecessary and objectionable, since it so materially increases the focal distance between the two.

Films of normal and abnormal blood may equally well be dealt with. One cover-glass is mounted on the slide with the film upwards, and the second cover-glass is mounted upon this with the film downwards, so that the films are in direct apposition.

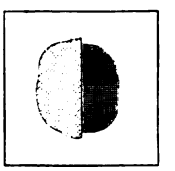
In such preparations a distinct microscopic interval will be found between the films, which dispels any chance of confusing the two. Such a method is not in any way a substitute for the usual blood count, but may be of service in class demonstrations, like the others described in this note.

Composite blocks.—A second plan of comparing abnormal with normal tissue in the same field of the microscope consists in having the two side by side. The result obtained by mounting two different sections side by side, cut from separate blocks, though each block has been trimmed so as to present one free straight edge uncovered by paraffin, is unsatisfactory. It is practically impossible to adjust the two sections so that the straight edges are microscopically in precise apposition; if so adjusted at one spot they will probably overlap elsewhere.

These drawbacks may be successfully obviated by cutting the sections from a composite block, *i.e.* from a block including the abnormal and the normal tissue.

Two blocks having been prepared in the usual manner, a perfectly flat face is obtained on one by cutting away with the microtome until the tissue is fully exposed. The microtome used should be one which cuts in an exact vertical and not in a curved plane. The face having been prepared, the block is removed from the carrier and cut through by hand in the same direction, but in a plane at right angles to the first, so as to expose a second area of the tissue embedded in the block. The second block having been similarly dealt with, the two blocks are lightly clamped together with those faces of the tissue in apposition which were previously cut with the microtome; a screw clip answers the purpose perfectly. The whole is then

FIG. 2.



Coronal view of composite block set for cutting.

held some way above a Bunsen flame for a few seconds with the roughly cut, exposed surfaces of the tissue downwards till the exterior of the paraffin softens.

The composite block is next removed from the clamp and finally placed (with the face, to be afterwards cut, downwards) in the usual brass mould, into which paraffin is then poured.

Such a block cuts without mishaps, the two portions of tissue remaining connected throughout the subsequent processes of fixing and staining.

The microscopic interval between the two pieces of tissue will be found uniform and straight, so that the line of apposition may be made to correspond precisely with the diameter of the field; and if the section is arranged on the slide with the junction horizontally the whole length of the tissues is easily brought under observation by means of the mechanical stage.

The specimens shown at the meeting of the Society comprised—a blood film from a case of pernicious anæmia directly superposed upon a normal film; $\frac{1}{12}$, Leishman's stain.

A section of leucoblastic marrow taken from the shaft of the femur in a case of suppurative diabetic gangrene and mounted directly upon a control section of adipose medulla from a normal femur; $\frac{1}{12}$, Leishman's stain.

A section of the precentral convolution from a case of general paralysis (prepared from a paraffin block kindly furnished by Dr. F. W. Mott, F.R.S., from a patient in Claybury Asylum) superposed upon a normal section from a corresponding spot; Leishman's stain.

A section from a composite block of normal kidney and kidney affected with chronic interstitial inflammation; hæmalum and eosin.

A section from a composite block of mammary carcinoma and chronic mastitis; Van Gieson.

November 1st, 1904.

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5. *Observations upon the acquirement of secondary sexual characters, indicating the formation of an internal secretion by the testicle.*[1]

By S. G. Shattock and C. G. Seligmann.

De notis sexus externis acquirendis.

Summarium.

Functio testis præcipua e spermatogenese constat. Insuper autem animalium quorumdam mas notis ex-

[1] Towards the expenses of this research a grant was made by the Council of the Royal College of Surgeons, and by the British Medical Association, on the recommendation of the Scientific Grants Committee of that Association. The paper, as here printed, is slightly modified from that communicated for the authors to the Royal Society by Professor J. R. Bradford, F.R.S., and published in the seventy-third volume of the Society's 'Proceedings.'

ternis acquisitis a feminâ distinguitur. Signa talia acquisita rationem habere ad testis actionem quamdam probat castratio.

Maxime nostra interest, tamen, dijudicare signorum pubertatis, quae acquiruntur teste ablato; quæ, teste intacto. In bovibus, exempli gratiâ, augescunt cornua in maribus castratis; sed apud hæc pecora feminae quoque cornua ferunt.

Experimenta nostra ex vasorum deferentium ligatione constant in gallo et in ovium quâdam varietate (Herdwick ut appellatur), in quâ varietate cornua mari adsunt, feminâ absunt.

In ove castratâ cornua non augescunt; post vasotomiam, ex contrario (vase utroque in locis duobus ligato et postea perscisso) ovis aspectum masculinum totum proponit. Similiter, pullo castrato, gallus nec cristam nec calcaria acquirit; sed vasibus deferentibus ligatis ac perscissis, nota externa omnia maris apparent. Testis ipse cujus occluditur vas, usque ad magnitudinem normatem augetur; scrutatio atque microscopica spermatogenesem abundanter demonstrat.

Glandula in pullo castrando nonnunquam dirupta est, fragmentis minutis in situ relictis, aut diversis in locis abdominis dislocatis. Fragmenta sic relicta crescunt donec, forsitan, testes duos normales magnitudine omnino æquant; et pullus nota externa proponit musculina. Horum fragmentorum illa dislocata glandulæ esse sine ductibus judicanda sunt.

Quae quum ita sint, signa externa, credere oportet, causari secretione "internâ" (ut dicitur) in his fragmentis formatâ; quia etsi in eis scrutatio microscopica spermatogenesem progredi ostendit, quum tamen in memoriam revocemus semen in conditionibus normalibus

emittendum esse, non huic secretioni " externae " ascribi debet metabolismus ille cujus effectus in notis externis maris propriis manifestantur.

The Problem Stated.

The question taken up in the present communication may be concisely stated as follows :

The most prominent and obvious function of the testicle is the formation of the sperm. Under normal circumstances this is discharged; it constitutes, that is to say, an external secretion.

In spermatogenesis the male attributes culminate. There is, however, another element in maleness, of a different kind, less essential, yet in many cases well pronounced, viz. the acquirement of certain external characters which distinguish the male from the female in many groups of living forms.

That the development of such secondary characters is related to some function of the testicle appears from the results which follow castration when carried out before the advent of sexual maturity. On what, then, does the production of these characters depend ?

It is conceivable that the result may be due to a nervous reflex arising out of the physical function of the sexual mechanism. This view our observations seem to us to disprove.

The genesis of the external male characters must, in our opinion, be transferred from the influence of the nervous system to the realm of chemistry. It depends, with more probability, upon the formation of a second secretion by the testicle, the absorption of which into the circulation induces the metabolic changes that reveal themselves as secondary sexual characters.

One method of experiment to which we may first allude, although the ultimate results were unsuccessful, consisted in the grafting together of two cockerels of the same age and breed, one of which had been previously castrated. The grafting was performed after the caponized cockerel had

FIG. 3.

The conjoined opposite legs of two immature fowls, the birds having been experimentally grafted together, one of the two having been first castrated and allowed to recover, the other being an intact cockerel of the same age and breed (Plymouth Rock). The skin was incised along the thigh and leg of each bird (under an anæsthetic), and the femora exposed and wired together by means of silver wire; the fibulæ were similarly secured together with silkworm gut; deep sutures were passed through the muscles in such a way as to bring the divided faces of those of opposite limbs together. The skin having been sutured, collodion was applied

over the edges of the wound, and the two limbs secured with a bandage. The knee-joints have been flexed so that the thighs are hidden from view at the back of the preparation; about half way down, however, the head of each femur may be seen appearing at the margin of the photograph. The specimen is now in the College of Surgeons' Museum, Pathological Series, No. 114A.

Pullorum duorum crus dextrum sinistrumque arte conjuncta, quorum pullorum alter castratus fuerat, alter integer erat. Ossa filo argenteo et musculi incisi suturis profundis conjuncta sunt. In omnibus talibus experimentis (in numero quattuor) alter ex duobus pullis post dies paucas, ac sine causâ manifestâ, mortuus est. Experimentum factum est ut probetur utrum pullus castratus nota externa masculina proponeret propter accessum ad pullum castratum sanguinis pulli integri.

quite recovered from the effects of the castration, *i. e.* after the wounds had thoroughly healed. The object of this experiment was to see whether the access of blood from the intact bird to the capon would lead to the development of external male characters in the latter, a positive result of which experiment would have shown the presence of an internal secretion in the blood reaching the capon, which secretion could only have been formed by the testicles of the intact cockerel. This experiment was carried out (under an anæsthetic) four times, but after a few days one of the pair, the capon, invariably died.

In the particular case of which the legs are figured on the other page, the two birds were grafted together by the opposite legs and thighs on September 24th, 1901. The shafts of the femora were wired together, and the fibulæ spliced with silk-worm gut; the muscles, which had been divided to reach the bones, were brought together with deep sutures; the skin of the opposed limbs was finally united by continuous suture, painted with collodion, and the grafted members secured with a bandage. The birds were kept in a large wicker basket, with a horse-shoe-shaped pillow to support the breasts. They remained in excellent condition, and fed themselves regularly together until October 2nd, *i.e.* the eighth day after the operation, when, without obvious cause, the capon died; the survivor was thereupon killed with chloroform.

The suggestion that an internal secretion might be elaborated by the "interstitial cells," which lie in groups between the tubuli, was put forward by one of us (S. G. S.), in 1897.[1]

The experiments to be now recorded were, in fact, primarily designed with the object of eliminating any part that might be played by the tubuli in this connection, and so of determining whether any function could be ascribed to the cells named.

They consisted in ligation of the vasa deferentia in the young of certain forms in which the male exhibits marked secondary characters.

It appeared possible that the epithelium of the testicular tubuli would, under these circumstances, on proliferating, undergo degeneration and atrophy from the pressure due to its own accumulation, whereas the interstitial cells of the

[1] 'British Medical Journal,' February 20th, 1897.

stroma might remain intact. This result, however, did not ensue, but others, which we venture to record as bearing on the problem under consideration.

The forms selected were a breed of sheep (Herdwick), the male of which is furnished with long recurved horns, of which the female is quite destitute; and the common fowl.

Observations upon Sheep.

We owe to the kindness of two friends the opportunity of observing many castrated sheep, as well as a certain number of others on which some form of obliteration of the vas deferens had been practised. Besides the horned (Herdwick) sheep already referred to, we made observations upon the hornless Southdown, in which the results, though less striking, are none the less constant.

The results of occlusion of the vasa deferentia in the Herdwick breed have to be compared with those following castration, and both with the normal standard. Lambs of the same age were selected, and the procedures mentioned were carried out at about the same time.

The occlusion of the vas deferens was effected a short way above the testicle by the application of two silk ligatures and division of the duct between. The animals were examined at different periods during their growth, and were killed when fully developed, at ages of from 10 to 14 months.

In those *castrated* either no horns appeared externally, and on preparation the skull exhibited only two low osseous tubercles or horn-cores, or very diminutive horns were produced, and beneath them a slightly more prominent core than in the first case, these differences being probably due to slight differences in the ages of the lambs when the testicles were removed.

In the *ewe* of the Herdwick breed there is no external trace of horn, nor does the prepared skull show any osseous core.

As contrasted with the results of castration, those of *vasotomy* are very striking. The horns attain their full size, and the skull its complete male characters, so that the head in no way differs from that of the normal or intact ram.

The form of the skull is modified by castration, not by double vasotomy, the modification in question being obviously correlated with the absence of horns.

FIG. 4.

The skull of a Herdwick ram, on which when a lamb castration had been carried out; the horns are represented only by two minute bony tubercles or cores. The figure also brings out the obtuse angle at which the portion of frontal bone in front of the orbit

joins that behind it. In the intact ram, and after vasotomy, the two portions of the frontal bone mentioned meet at a right angle. This and the following sheep were born in the same lambing season in one herd, and were within a week or two of the same age. Specimen in the Museum of the Royal College of Surgeons, Physiological Series.

Ovis adultæ cranium cujusdam varietatis (Herdwick ut appellatur) in quâ varietate cornua mari adsunt feminâ absunt. Agnus castratus erat antequam cornua apparuerant: haec postea non creverunt.

The skull of the castrated sheep, or wether, is less rugged, and the bones thinner, but besides such general differences the plane of the os frontis is continued backwards behind the orbits at a very obtuse angle.

In the intact ram, and equally after vasotomy, the plane of the frontal behind the orbit lies almost at a right angle with the interorbital portion of the bone, the horn-cores arising from the upper or horizontal area.

Although the skull generally is thicker in either case than in the wether, this alone does not account for the difference in external form, seeing that the cranial cavity presents a corresponding extension in the frontal region.

In the configuration of its skull, as in the absence of horns, the castrated animal precisely resembles the hornless ewe of the breed.

We have studied the effects of the same procedures upon sheep of a well-known pedigree Southdown herd. The result in such animals is less striking than in the Herdwick, partly because each sex is hornless, and partly because amongst Southdowns individual variations in the form of the head are not uncommon: thus, whilst the head of the wether usually offers a marked contrast to that of the ram, in certain cases the characters of the two so nearly approximate that even an expert may find it difficult to distinguish between them, the ram under such circumstances being commonly called "wether-headed."

In the Southdown there is not (as in the Herdwick) any marked difference produced by castration in the form of the forehead, the angle between the pre- and post-orbital portions of the frontal bone being equally obtuse in the vasotomised sheep and the wether, and this for the reason that both are equally destitute of horns.

That the occlusion of the vas had been complete in all the cases observed was proved by a careful dissection of the testicles after the animals were killed.

Seeing that the full development of male characters proceeds in spite of double vasotomy, it becomes interesting to inquire into the condition of the testicles and into the sexual physiology of the animals themselves.

To take the latter first. A Southdown, the subject of double vasotomy when a lamb, and kept apart until full grown from

FIG. 5.

The skull of a Herdwick ram on which when a lamb the vasa deferentia had been tied and cut through before any horn had made its appearance. The horns have grown to the full size. This and the preceding sheep were born in the same lambing

season in one herd, and were within a week or two of the same age. Specimen in the Museum of the Royal College of Surgeons, Physiological Series.

Ovis adultæ cranium cujusdam varietatis (Herdwick ut appellatur) in quâ varietate cornua mari adsunt, feminâ absunt. Testis utriusque vas ligatum est in locis duobus et postea perscissum, antequam cornua apparuerant. Testes cornua quoque ad normalem magnitudinem aucta sunt. Sectio testis microscopica spermatogenesem insigniter progressam fuisse demonstrat.

any female, was turned loose with a couple of maiden ewes; he at once copulated, erection and intromission being complete. The two ewes were not again admitted to the flock, but were kept apart, with the result that neither afterwards proved to in lamb. This animal was killed 18 months after the vasectomy. The testicles had, from the first, grown symmetrically, and had reached the normal size; dissection revealed a complete interruption of each vas close above the gland.

In certain cases one of the testicles underwent a marked diminution, *i.e.* it not merely failed to grow, but rapidly wasted. In the other cases both organs attained the full dimensions. These differences are to be ascribed to differences in the condition of the blood supply; when the vas is cleanly isolated and divided after ligation without the inclusion of vessels, or without the subsequent occurrence of thrombosis, no atrophy of the gland ensues. When atrophy of one testicle arises, the other suffices singly to bring about the full development of the male characters.

A careful dissection, carried out in all the cases of vasectomy examined and cited, showed that the vas had been completely occluded; not only was its continuity interrupted, but the noose of the ligature was demonstrated on the end of each segment of the divided duct. The epididymis after occlusion of the vas may become notably larger than normal; this is especially obvious in the lower end or globus minor, and is to be ascribed to its over-distension with the secretion transmitted from the body of the gland.

Microscopic sections of the testis of the normal adult Herdwick sheep and of that from the vasectomised animal of the same age, and killed at the same date, show similar histological pictures. The tubuli are filled with epithelial cells, and in nearly every tube spermatogenesis is in progress.

In the case of one of the Southdown sheep subjected to double vasectomy, and in which each testicle grew to the full size, the animal was allowed to live over nineteen months. Histological examination proved the tubular structure of the testicle to be quite normal, with spermatogenesis in active progress.

In the sheep the secondary effects produced by double castration and double vasectomy upon the prostate gland are difficult to observe, since this gland, though occupying the usual position near the neck of the bladder, lies hidden from sight (as it does in the pig) between the urethral mucosa and the thick sheath of urethral muscle.

FIG. 6.

One of a testicles of a Herdwick ram on which vasectomy was performed and the skull of which is shown in the preceding figure. A short way above the level of the testis there is a deficiency in the vas about an inch in length, the duct having been ligatured in two places and a piece excised between. As compared with the normal testis of

an adult ram of the same breed, the body of the organ is of the full size. The globus minor is much enlarged from the accumulation of secretion, but except at one spot near the origin of the vas the convolutions of the epididymal tube are evident on the surface. The segment of the vas on the distal side of the occlusion is notably larger than that on the proximal. Microscopic examination of the body of the gland showed spermatogenesis to be in active progress. Specimen in the Museum of the Royal College of Surgeons, Physiological Series.

Ovis præcedentis testiculus, vase deferenti ligato et postea perscisso. Globus minor secreto retento distenditur.

Cowper's glands, on the contrary, form two conspicuous objects, one on either side, behind the bulb of the urethra. In regard to them it may be remarked that whilst in the castrated lamb they fail to grow, in the lamb submitted to vasectomy the glands come to equal in size those of the intact ram. The same is true of the vesiculæ seminales. If one testicle is removed and the vas of the other ligatured and divided, Cowper's glands and the vesiculæ acquire the full size, and this without asymmetry. The following specimens illustrating these observations have been placed in the Museum of the Royal College of Surgeons, Pathological Series.

25A. The bladder with the urethra as far as the penile portion, together with the vesiculæ seminales and terminal portions of the vasa deferentia of a Herdwick sheep which was castrated as a lamb in June 1902, and killed in July, 1903.

The vesiculæ are quite diminutive, not more than three quarters of an inch in length, and a quarter of an inch where widest; the terminal parts of the vasa deferentia exhibit a corresponding failure of growth, being less than half the normal diameter.

There is a marked failure, moreover, in the development of Cowper's glands, these bodies with their investing musculature measuring, each, only 7 mm. in diameter.

The urethra, though of full length, is of lesser diameter than in the intact fully grown ram, from a diminution in the thickness of its muscular wall.

The condition of the prostate gland, which lies completely hidden between the muscular wall of the urethra and the urethral mucosa, is not shown.

25B. The parts of a fully grown Herdwick sheep, corresponding to those shown in the preceding specimen. Each vas deferens was tied when the animal was a lamb. As compared with a dissection of the organs from a fully grown intact ram of the same breed, the vesiculæ, the terminal parts of the vasa deferentia, and Cowper's glands have attained the full size, and the urethra its full muscularity and diameter.

The development has proceeded quite symmetrically, although one testicle underwent atrophy after the operation (probably from interference with its blood-supply); the other testicle attained its full development.

25c. The similar parts of a fully grown Southdown sheep, on which, when a lamb, vasectomy was carried out on one side, and castration on the other.

The vesiculæ, terminal parts of the vasa deferentia, Cowper's glands, and the urethral wall have all attained the full development, and symmetrically so on the two sides.

In other cases of double vasectomy both testicles attained the full size, the condition of Cowper's glands and of the accessory structures being one of similar complete development.

Experiments upon Fowls.

Even still more striking are the results of double vasectomy in the cockerel of the common fowl. In the fully grown cock the exposure of the vasa deferentia and their ligation is not particularly difficult, but in the young bird it is otherwise; and the results cited are limited to those cases where careful dissection afterwards proved that this difficult procedure had been successfully carried out, the continuity of the duct being found interrupted, and the nose of the ligature discovered at the site of the operation. The method of proceeding was as follows:— The vas is exposed in its course over the kidney by a curved incision carried through the lateral wall of the abdomen; the duct, having been ligatured as near to the testicle as possible, is then cut across a short distance below the ligatured spot, no ligature being placed on the lower segment. The vas of the other side is afterwards similarly dealt with through a second incision carried through the corresponding side of the abdomen. Owing to the difficulties of this operation, vasectomy was in some cases performed on one side only, the testicle of the other being removed. The anæsthetic used was chloroform, and the material of the ligature, silk.

The results of double vasectomy, or of one-sided vasectomy combined with one-sided castration, are in all cases alike. When carried out upon the young, immature bird, or cockerel, the development of the male characters proceeds without any notable interruption, and reaches its full degree.

The birds used in the experiments were so young that it needed an expert to determine their sex: examination, moreover, of the testicles removed from cockerels subjected to the

combined castration-vasectomy just referred to, as well as of those removed from birds of the same brood, showed that no spermatogenesis had arisen at the age selected for operation. We may adduce examples in order to give the full grounds for the general statement set forth with regard to these experiments.

Double vasectomy.—Impure Plymouth Rock, 7–8 weeks old. Nine months after the operation the head was male in type; neck-hackles well developed; tail beginning to assume male characters; spurs indicated. Twelve months after the date of operation the spurs were stout, though short; head thoroughly male; neck- and saddle-hackles moderately well developed; tail short, male in kind, with sickle feathers.

The bird remained in the same condition, and was killed twelve months after the date of the operation. At the autopsy the testicles were found to be of full size (about that of a pigeon's egg), and in their general aspect quite normal. In connection with the right there was a spermatocele about as large as a haricot bean; this, on being punctured, gave exit to a whitish fluid which microscopically showed numerous spermatozoa, some of them motile. The superior segment of the divided vas, or that in connection with the testicle, was dilated; the upper end of the lower segment was traceable into scar tissue, in which it terminated. On the left side there was no spermatocele in connection with the gland, but the convolutions of the epididymis were abnormally evident. On each side the noose of the silk ligature was found *in situ* on the upper segment of the vas, above the level of the lower border of the testicle.

As a second instance we may recount the following:

Double vasectomy.—"Plymouth Rock, about 8 weeks old. In the summer of the year following the operation the head and neck-hackles were typically male, saddle-hackles fairly so; tail short, carried almost vertically, contained a number of short curved feather; spurs short and stout. In the winter of the same year the neck- and saddle-hackles were typically male; tail short, bushy, feathers curved; spurs long and sharp. The bird was killed in the spring of the following year. Dissection showed the left testicle to be of full size, 4 cm. in the longer diameter: in connection with the upper end of the epididymis is a retention cyst filled with white secretion, and about 1 cm. in diameter; the epididymis is, as a whole, enlarged from disten-

sion. The upper end of the lower segment of the vas terminates a short distance above the lower border of the testicle. The ligature lies *in situ* on the end of the epididymal segment of the vas, which is separated by a distinct interval from the other.

The right testicle is slightly smaller than the left, the epididymis distended, and the continuity of the vas interrupted; the

FIG. 7.

Portion of the trunk of the fowl referred to in the text upon which double vasectomy was performed when the bird was about eight weeks old. The testicles are of about the full size and of normal form. The vas deferens of each side was tied near the testicle and divided a short way below the ligature. The right testicle has been displaced towards the middle line in order to bring into view the area of operation. The distal, lower segment of the vas terminates abruptly at the spot marked by a glass rod: between this and the ligatured proximal segment there intervened a distance of about 8 mm. The ligature still remains on the proximal end of the duct, thinly covered with connective tissue. On the left side examination disclosed an almost precisely similar condition of the parts concerned, the want of continuity in the vas deferens being quite as distinct as on the right. Specimen in the Museum of the Royal College of Surgeons, Physiological Series.

Trunci portio galli in quo utrumque vas juxta testem, ligatum et postea perscissum est, antequam nota sexus externa apparuerant. Testis uterque ad magnitudinem normalem auctus est: pullus nota omnia externa masculina proposuit.

ligature lies *in situ* on the lower end of the upper segment of the duct (Fig. 7).

As an example showing the results of unilateral vasectomy combined with unilateral castration we may select the following:

Buff Orpington, about 8 weeks old. Nine months after the operation the bird was thoroughly male, the comb and wattles being well developed, as well as the neck-hackles and sickle-feathers of the tail.

Twelve months after the date of operation the spurs were sharp. On being put with a hen the bird immediately copulated, although it had had no previous opportunity of approaching one. Eighteen months after the operation it was killed. On dissection the right testicle was found to be of full size, about 3·5 cm. in the longer diameter; the epididymis was slightly distended. A scraping from the divided body of the gland revealed the presence of spermatozoa. The lower segment of the vas was found to taper off and end quite distinctly about a quarter of an inch below the level of the testicle. The noose of the ligature was covered with a thin layer of connective tissue, and lay on the posterior surface of the organ. The position of the ligature may be explained by the general growth of the gland; this growth would naturally lead to an extension in all directions, and that in the downward direction would, relatively to the testicle, raise the site of the ligature. On the left side no trace of testicle was found.

Microscopic examination of the body of the testis from the case of double vasectomy first cited shows the tubuli to be full of cells, and spermatogenesis in high activity, all the typical histological pictures being present. The same holds true of the right testicle from the case of combined vasectomy and castration last detailed.

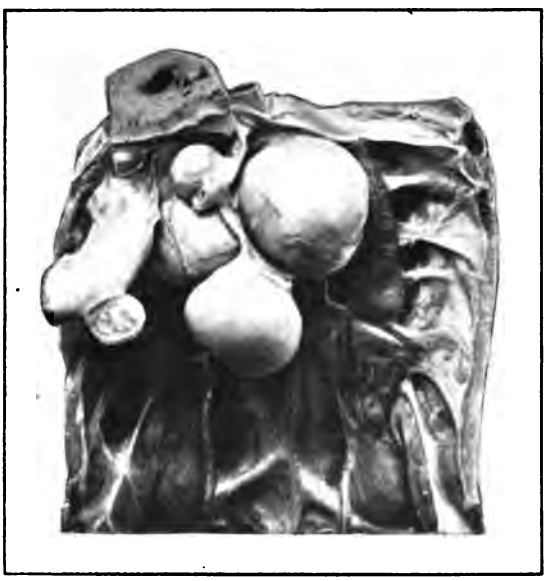
These results offer a striking contrast to those following a double castration when carried out upon the immature bird. Double castration was performed through a lateral incision on each side, the testicle being exposed to view, and afterwards carefully disconnected from its attachments with fine forceps, and withdrawn. In ideal experiments the gland was withdrawn entire; in others rupture occurred during the process of detachment, the organ being then removed piecemeal.

Results of incomplete caponisation.—In certain of our experiments it happened that the testicle gave way during its detachment, and that minute fragments were unintentionally

left behind. Sometimes such remnants, as told by subsequent dissection, were left in their normal position; at others they were dislocated and transplanted upon the adjacent viscera, or abdominal wall. Under such circumstances the cockerel assumed in different degrees the character of the male.

The actual number of gland remnants left at such imperfect operations, and the position of the grafts resulting from their

FIG. 8.



Portion of the abdomen of the bird referred to in the text, showing the grafts due to the unintentional transplantation of minute fragments of the testicles in caponisation. On the left-hand side is shown a coil of intestine to which an oval graft about the size of a pea is adherent; this graft has been divided so as to appear in section. At the highest point of the coil may be seen a portion of a smaller graft connected with the under side of the remnant of liver preserved in the specimen. The various other larger masses on the right-hand side of the coil consist equally of testicular tissue. Specimen No. 99D, Royal College of Surgeons' Museum, Pathological Series.

Trunci portio galli castrati in quo fragmenta testiculorum minuta relicta sunt. Pullus castratus nota omnia externa masculina proposuit. Post mortem noduli plures magnitudinis diversi in abdomine inveniti sunt, qui noduli ex telâ testiculari constant. Ex illis unus ad intestinum, alius ad superficiem inferiorem jecoris, adhæret.

displacement, varied considerably. Thus in one case the dissection of the fully grown bird, which had been castrated when

from 6 to 8 weeks old, showed on the left side a spheroidal mass of testicular substance, 2 cm. in diameter, lying in front of the upper part of the kidney, and into the lower end of which the vas deferens is directly traceable. Hanging in the mid-line from a loose "mesorchium" is a spheroidal graft 1·5 cm. in diameter. On the right side there is a bilobed mass 2·3 cm. in the chief vertical diameter, with the lower end of which the right vas is directly connected; closely adherent to the front of the upper lobe of this, though slightly movable over it, is a spheroidal mass 0·6 cm. in diameter. A further oval nodule 0·7 cm. in chief diameter is closely adherent to the surface of a coil of the small intestine in the neighbourhood of the liver; a scraping from this graft when cut through in the recent state showed large numbers of spermatozoa. Lastly there is a graft of about the same dimensions intimately adherent to the under surface of the liver itself. The external characters acquired by this bird were fully male throughout.

The microscopic sections of the graft which adheres to the under surface of the liver, show the typical pictures of active spermatogenesis, considerable numbers of spermatozoa lying free, moreover, in the lumen of many of the large tubuli which compose the nodule.

It may be remarked, in passing, that such scattered grafts do not bear classifying with glandular tumours or adenomata, since they do not grow independently of the general requirements of the body. For the whole sum of a series of such grafts and hyperplastic remnants does not exceed the volume of the two fully developed testicles. In this the remnants behave like those of thyroid tissue left experimentally after partial excision of the thyroid gland; or as do the dormant accessory thyroids after the complete removal of a goitre, when the accessory gland after attaining a certain size ceases to increase further; or the process, again, resembles the reproduction and hyperplasia of hepatic tissue which follows partial excision of the liver, of a fourth or even half its bulk.[1]

Much less can such grafts be viewed as carcinomata, a matter of some interest in connection with the heterotypical mitosis which has been observed in the cells of carcinomatous

[1] Ponfick, 'Centralblatt f. Med. Wiss.,' 1894; Von Meister, 'Centralblatt f. Allg. Path. und Anat. Path.,' 1891.

tumours by Professor Farmer, Mr. Moore, and Mr. C. E. Walker ('Proceedings of the Royal Society' December, 1903, and 'Transactions of the Pathological Society,' vol. lv, p. 449).

The great feature of carcinoma is its invasiveness, and the presence of heterotypical cell division does not *per se* explain this phenomemon.

In the foregoing examples of incomplete caponisation the cells

FIG. 9.

A microscopic section of the marginal portion of the graft shown adhering to the liver in the foregoing figure. On the lower right-hand border is the adjacent hepatic tissue, separated by a narrow line of connective tissue from the substance of the graft. The latter consists of testicular tubuli distended with cells, and in which active spermatogenesis is in progress, many spermatozoa lying free in the lumen of the tubules.

Sectio microscopica noduli ad superficiem jecoris inferiorem adhærentis. In parte dextrâ monstratur capsula telæ cellulosæ inter telam hepaticam et telam testicularem. Spermatogenesis insigniter progreditur.

concerned belong to the particular type in question, viz. the "reduced," in which the number of chromosomes is only half that in the somatic cell. Nevertheless, the proliferation results, not in an invading neoplasm, but in a circumscribed formation of normal testicular tissue, the whole amount of which produced

does no more than replace or regenerate the two normal glands.

In the most perfect cases of reproduction each gland attains its full normal size. A bird was castrated when quite young, 6–8 weeks old. Six months later the comb and wattles presented a medium degree of development; the spurs were very small. Nine months after the date of operation the spurs were still small, and the general male characters ill developed. Twelve months after the operation the spurs were short but stout. Seventeen months after the operation the comb and wattles were thoroughly male, the neck- and saddle-hackles fully developed, and the spurs long, stout and sharp.

The bird was killed 21 months after the date of the operation. Each testis was found to be of normal form and full size, the epididymis well pronounced, and without retention cysts. Each vas was in every respect normal and filled with white secretion, which microscopically showed countless actively moving spermatozoa. The history, as above given, shows a marked delay in the development of the male characters, and indicates that these developed *pari passu* with the reproduction of the testicles, until they ultimately became fully pronounced.

That a comparatively small volume of testicular tissue will suffice to bring about the development of male characters appears from the following result, in which the bird grew to be fully male, with the slight exception that the neck-hackles were somewhat less closely set than is normally the case.

A Buff Orpington, of about 8 weeks, at which time double castration was performed. Eight months after the operation the comb was well developed and bright in colour; the plumage in general somewhat pale and sparse; neck-hackles moderately developed; spurs small. Eleven months after the operation the comb and wattles were well developed; neck-hackles moderate; saddle-hackles fairly male; tail feathers beginning to take the male curve; spurs grown to the normal male extent.

The bird was killed 17 months after the operation, its condition being as last noted. Dissection shows on the left side no trace of testicle in its normal position, but an inch and a half lower down, and three quarters of an inch anterior to this spot, there is an oval graft 2·5 cm. in chief diameter, loosely connected with the lateral wall of the abdomen. Above it,

separated by a distance of 1·5 cm. and intimately incorporated with the peritoneum, is a second graft 0·5 cm. in chief diameter; and behind or dorsally to this is a further minute nodule 0·2 cm. in diameter, and likewise inseparably adherent to the peritoneum.

The vas is extremely fine and traceable to the vacant original site of the testicle. On the right side, in the situation of the testis, there are two small flattened nodules, the larger, lower, of which is 0·8 cm. in chief, vertical diameter. Into the lower end of the inferior the vas, diminished in size and empty of secretion, is directly traceable. A third nodule, which lay about 1 cm. anteriorly to these and slightly lower in the abdominal cavity, was removed for microscopic purposes; scrapings from its divided surface disclosed the presence of spermatozoa.

Histologically the largest graft (that on the left side of the abdomen) shows closely applied tubuli of full size, every one of which presents the histological pictures typical of active spermatogenesis. The lumen of the tubuli contains free spermatozoa. All the cell nuceli are throughout perfectly stained with nuclear dyes, proving that the tissue is living and not in an obsolete or necrotic condition. The amount of intertubular stroma is very small, and supports well-formed arterioles and other vessels.

The much greater size of the dislocated graft on the left side of the abdomen, and its high state of activity, suggest that it is the chief element concerned in the production of the male characters. This graft is strictly ductless, and is, moreover, entirely disconnected from its proper nervous relations.

But much smaller grafts than any of these may be met with in imperfect castration, and in such circumstances the male characters are correspondingly ill pronounced. One must, in fact, regard the external character of maleness as a quantity which varies proportionally with the amount of gland-tissue present—at least in regard to certain of its manifestations, viz., the comb and wattles.

Conclusions.

From the fact that in the young of the Herdwick sheep and fowl, occlusion of the vasa deferentia does not inhibit the full acquirement of secondary male characters, it is clear, in the first place, that the discharge of the sperm is not in any way

the factor responsible for the production of the characters referred to.

This conclusion admits of being extended to mean that the production of secondary characters is not due to metabolic changes set up by a nervous reflex arising out of the mere physical function of the sexual mechanism. This is made still more forcible by the results of incomplete caponisation in those cases where the grafts were found in situations far removed from the normal, and altogether disconnected from the nerve supply proper to the testicle in its natural position and connections.

Such grafts, devoid as they are of any channels communicating externally, and consisting as they do of tubuli only, are virtually ductless glands, and the metabolic results arising from their function must, as in analogous cases elsewhere, be attributed to the elaboration of an internal secretion and its absorption into the general circulation.

What particular cell elements are concerned in the production of such a secretion cannot as yet be stated. Various possibilities arise which demand the test of further experiment.

The function of spermatogenesis, although not itself the whole or sufficient cause, may be the initial factor of a dual or even a more complex process.

It is quite within the bounds of possibility that certain of the epithelial cells within the tubuli may produce a pro-secretin such as is produced within the intestinal epithelium; that the chemical changes accompanying spermatogenesis in other of the cells of the tubule may lead to the conversion of this pro-secretin into a secretin, much as the acid chyme does in the case of the pro-secretin present in the intestinal cells; and that the secretin so formed may, without being shed into the lumen of the tubule, be transferred to the lymph spaces, and thus eventually reach the general circulation, and incite those metabolic changes in distant parts of the body which disclose themselves as secondary sexual characters. The intimate connection that arises in the process of spermatogenesis between the spermatoblasts and the "sustentacular" cells is a phenomenon not yet explained; This phenomenon possibly coincides with the interaction suggested.

In regard to the interstitial cells of the stroma, they have

characters so unmistakably glandular that some secreting function, probably a sexual one, must be assigned to them, and they may, of course, take a part in the elaboration of such a secretion as that suggested.

But the great variation in the proportion of such cells present in different forms of mammals makes it difficult to formulate any hypothesis to test by way of experiment, and we are not as yet in a position to make any statement in regard to them.

In the pig these cells are in such amount that they form what may be viewed as a second glandular element interpenetrating the tubular portion—a paratubular gland.

In conclusion, we may point out the importance of distinguishing in such problems as those discussed, between such external characters as are acquired independently of the growth of the testicle after birth and such as are dependent upon the latter. In bovines, for example, the growth of the horns is not cut short by castration as it is in the Herdwick sheep selected for our experiments. Here, however, we have to bear in mind the fact that the female is equally well furnished with horns. The horns of the bull, therefore, though they may be marks of maturity, cannot be regarded as attributes of maleness. Into the wide subject here open for speculation we do not at present propose to enter.

Furthermore, it must be borne in mind that the sexes may acquire at puberty certain external characters which depend upon the integrity of the sexual glands, and are yet common to both.

In the human subject, *e.g.*, the growth of pubic and axillary hair is a mark of puberty common to the two sexes, whilst that on the face characterises the male. In this case the results of castration show that the growth of hair in these several positions is to be ascribed to some function of the sexual glands. The acquirement of external sexual characters common to the sexes is best harmonised by the theory of the common origin of sex through an hermaphrodite ancestry; such characters would seem to indicate the formation of an internal secretion by the testicle and ovary of a like kind, and in this degree point to a common function of the sexual glands.

We have to acknowledge our indebtedness to Mr. George Jonas, of Duxford, for much technical information; to Mr.

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6. *The results of castration and vasectomy upon the prostate gland in the enlarged and normal condition.*

By CUTHBERT S. WALLACE.

Castration as a remedial measure.

AT a meeting of the American Medical Association held in 1893, J. W. White, of Philadelphia, with great diffidence, proposed castration as a remedy for the senile enlargement of the prostate. He himself was doubtful of the morality of the operation, and was by no means sure in what spirit the proposal would be received by the profession in general.

At this date prostatectomy had, according to White, a mortality of 13·6 per cent. for the perineal method, and 25 per cent. for the suprapubic. Mansell Moullin is also quoted as giving a mortality in 95 cases of 20 per cent.

It was the unsatisfactory condition of the operative treatment of prostatic enlargement that induced the search for other methods. The shrinking of uterine fibroids after removal of the ovaries suggested to White that, although the uterus and prostate were not true homologues, removal of the testes might be followed by atrophy of the prostate.

With a view of observing the effects of castration on the normal adult prostate, White conducted a series of experiments on dogs. He satisfied himself that atrophy of the normal prostate followed castration with remarkable rapidity and sureness. He therefore felt himself entitled to suggest castration as a treatment for prostatic hypertrophy.

In April, 1893, Fredrik, the Norwegian who had noted the atrophy of the prostate after castration, performed the operation with the purpose of producing an atrophy of the enlarged prostate. This fact was unknown apparently to both White and Harrison.

In September ('British Medical Journal,' September 23rd, 1893) R. Harrison proposed vasectomy as a substitute for castration; he was induced to make this suggestion, having noted atrophy of the testis to follow accidental division of the vas in an operation for varicocele. He further stated in the same letter that he had actually put this suggestion into practice in the case of a gentleman who wished to be castrated for an enlarged prostate.

In 1893 the operations of castration and vasectomy were initiated for the relief of enlarged prostate and seem to have found very general acceptance both in Europe and America.

In 1894 the results of such operations began to be published.

Castration.—The following, a favourable example, was published in the 'British Medical Journal,' November 3rd, 1894, by Mansell Moullin. A man, aged 81 years, had been the subject of several attacks of retention. The prostate was enormously enlarged as felt *per rectum*. Supra-pubic cystotomy was performed, but the patient went downhill until the fourteenth day, when castration was performed. The following day urine passed freely by the urethra. In three weeks' time the prostate was only represented by a fusiform thickening. A further reference will be made to this case.

In 1895, at the meeting of the American Surgical Association, J. W. White published 111 cases of castration for enlarged prostate. The results are as follows:

87 per cent. were followed by a more or less rapid atrophy or shrinking of the prostate.

52 per cent.: Cystitis improved or cured.

66 per cent.: A return of vesical contractility occurred in more or less degree.

83 per cent.: Amelioration of symptoms.

46 per cent.: The local condition became nearly normal.

7 per cent. mortality.

There were actually 20 deaths in the 111 cases; but 13 fatal cases, in which there were symptoms of uræmia before operation, were not taken into account in reckoning the percentage mortality.

In 1896, before the American Surgical Association, A. T. Cabot read a paper entitled, "The Question of Castration for Enlarged Prostate." Sixty-one cases were analysed (none of

these were included in White's paper). The results are as follows:

9·8 per cent.: Failures.

6·6 per cent.: Moderate improvement.

83·6 per cent.: Substantial improvement.

19·4 per cent. mortality (all fatal cases included).

In the same year (1896) Professor Bruns, of Tubingen, collected 93 cases; how many are included in the foregoing tables it is impossible to say. In 83 per cent. the prostate decreased in size. In many cases aggravated cystitis was improved and occasionally cured. In 28 cases, in which the catheter had been used from a few months to two years, voluntary micturition was restored in 22 (78 per cent). Again, in 20 cases in which catheter life had lasted two to twenty years eight patients were enabled to discard the catheter entirely.

In 1900 A. C. Wood published in the 'Annals of Surgery' 143 cases of castration for enlarged prostate; White's and Cabot's cases were not included. The results were as follows:

143 cases; deaths, 13.

51·5 per cent.: Decrease in the prostate noted.

3 per cent.: Definite statement of no decrease. (In one case there is said to have been a definite increase.)

90 per cent.: Benefited.

.57 per cent.: Urination improved.

18·5 per cent.: Cystitis relieved.

4·6 per cent.: No improvement definitely stated.

9·09 per cent. mortality.

Vasectomy as a remedial measure.

At the same meeting of the American Medical Association in 1895, at which he published the first series of castrations, White alluded to vasectomy as a treatment for enlarged prostate, and detailed some experiments which he had made to test the effect of vasectomy on the prostate. White at this time fully recognised the fact that the integrity of the vas was not essential to the nutrition of the testicle.

In 1900 A. C. Wood published in the 'Annals of Surgery' 193 cases of vasectomy for enlarged prostate. The details in most cases are said to have been meagre. The results are as follows:

9 per cent.: Decrease in size of the prostate.

15 per cent.: Improved urination.

5 per cent.: Cystitis improved.

67 per cent.: General improvement.

15 per cent.: No improvement.

6·7 per cent. mortality (the deaths arose from kidney complications and carcinoma of the prostate).

The article ends with the following expression of opinion: "The figures here set forth furnish in the opinion of the writer ample reason for advising and performing one of these operations [castration or vasectomy] in suitable cases."

Results of castration and vasectomy compared.

If the foregoing tables are compared it will be seen that the results claimed for castration and vasectomy are very similar as regards "general improvement." "Shrinkage" of the prostate and return of urinary function seem to have been more marked after castration than after vasectomy. The comparative mortality is harder to arrive at, since in some series the fatal cases are reduced by the subtraction of cases that are said to have shown uræmic symptoms before the operation was undertaken.

Year.	Author.	Number.	Deaths.	Percentage mortality.
Castration—				
1895	White	111 cases	7 or 20	7, or 18·02 per cent. (with all fatal cases included).
1896	Cabot	61 „	15	19 per cent. (all cases included).
1900	Wood	143 „	13	9·09 per cent.
Vasectomy—				
1900	Wood	193 „	—	6·7 per cent. (all cases included).

As regards mortality vasectomy has the advantage over castration.

If all the fatal cases are taken into consideration in arriving at the mortality, it will be seen that castration is very little less dangerous than prostatectomy, according to the figures supplied by White and Mansell Moullin. Thus:

Operation.	Mortality.
Prostatectomy	(*Circa*) 13 per cent.; 25 per cent.; 20 per cent.
Castration	(*Circa*) 15 per cent.
Vasectomy	(*Circa*) 7 per cent.

In reading over the cases collected in the foregoing tables

(castration and vasectomy) one cannot fail to be struck by the fact that very few of the cases ended in a complete cure. By far the greater number were simply improved and the frequency of micturition reduced. When it is remembered how often cases of prostatic enlargement are greatly improved by rest and treatment of the accompanying cystitis, it is an open question whether the results above set forth were not to a considerable measure due to such treatment. It will be of interest if at this point the recorded observations on castration and vasectomy are briefly reviewed.

Experimental evidence of the effects of double castration.

In 1775 John Hunter made his classical observation on the hypoplasia or want of development of the prostate that resulted from castration in youth or infancy. The knowledge that castration in adult life causes an atrophy of the prostate seems to rest on the observation of Griffiths, White, and Guyon.

Griffiths published his first result in the 'Journal of Anatomy and Physiology' (1889–1890). He examined the prostate of a dog which had been castrated when two years old and killed after an interval of a year. It was stated that the organ was small, and to all purposes as atrophied as if the dog had been castrated in youth.

In the spring of 1893 J. W. White conducted his experiments. He castrated numerous dogs and examined their prostates after varying intervals. The results are as follows:

No.	Interval between castration and death in days.	Weight of prostate after castration in grammes.	Loss of weight of prostate in grammes.	Weight of dog in kilos.
19	17	5·420	9·580	15
21	21	5·700	8·300	14
20	30	2·600	11·400	14
4	32	2·600	17·380	20
16	41	5·700	9·300	15
13	54	4·420	26·580	31
14	54	2·700	20·300	23
24	60	1·500	13·500	15
9	61	4·000	18·000	22
25	65	4·500	20·500	25
5	—	3·920	22·680	26

In experiment 19 there was no microscopic change found, in experiment 21 commencing changes in the epithelium only. In experiment 20 glands showed distinct signs of atrophy and were separated by much connective tissue. In experiment 16 gland tissue but slightly affected, muscle-fibres all atrophied. In experiment 9 remains of glands showed closely packed cells. In experiment 25 atrophy of both muscle and gland tissue.

It will be seen that there is no constant relation between the amount of muscular or glandular atrophy and the length of time that had elapsed between the experiment and the examination of the organ. Thus in experiment 20 there was distinct glandular atrophy after an interval of thirty days, but very little alteration in this tissue in experiment 16 after an interval of forty-one days. Experiment 19 is also remarkable in that the gland showed no microscopic change and yet had lost 9·58 grammes in weight. The result will form the subject of comment later on in this paper.

Guyon (1895) found that there was marked decrease in the bulk of the prostate within five months of double castration; after an interval of two and a half months the atrophy was well established. The gland tissue was markedly atrophied even after the shorter interval.

In 1895 J. Griffiths castrated a dog aged between three and four years, and examined the prostate after three weeks. The organ was stated to be small, the tubules to be reduced in size and number. In many places the cells filled the lumen, the columnar cells were replaced with cubical, and hardly a trace of muscle-fibres was left.

Experimental evidence of the effects of double vasectomy.

John Hunter[1] made the observation in the human subject that the testicle developed and contained spermatozoa, although there was no connection between the testicle and its excretory canal, the vas.

Some years later, in 1825, Astley Cooper performed the following experiment on a dog. He divided the vas on one side and on the other the vessels of the cord. The testicle on

[1] Hunter's 'Works,' edited by Palmer.

the latter side sloughed, but the testis with a divided vas increased slightly in size. In 1826 the dog was seen *in coitû*, but the bitch was not fertilised. Four years later (1829) the dog was killed. The epididymis was found full of spermatozoa retained by the occlusion of the vas. The testis was normal in other respects. The specimen is now in the museum of the Royal College of Surgeons (No. 4289), and shows the remains of the sloughed testicle on the one side and a testis of normal size on the other. This preparation is figured in Astley Cooper's work on the testis.

Mr. Shattock has recently examined this testicle by means of microscopic sections; he finds the tubuli to be of normal size, and full of epithelial cells which diminish in size towards the centre, when they are intermingled with considerable numbers of spermatozoa.

In 1842 Curling repeated this experiment, and found that in cats and dogs interruption of the continuity of the vas did not interfere with the process of spermatogenesis. In four experiments the length of time between the section of the vas and the examination of the testis varied from sixty days to eight months.

Gosselin, again, in 1853 performed vasectomy on dogs, and found the testes normal after four and six months respectively.

Within the last few years J. Griffiths has once again shown that vasectomy does not hinder the growth of the testis in youth or interfere with the production of spermatozoa in adult life. He has demonstrated, however, that interference with the blood-supply may have very serious effects on the testis, and even cause its complete atrophy.

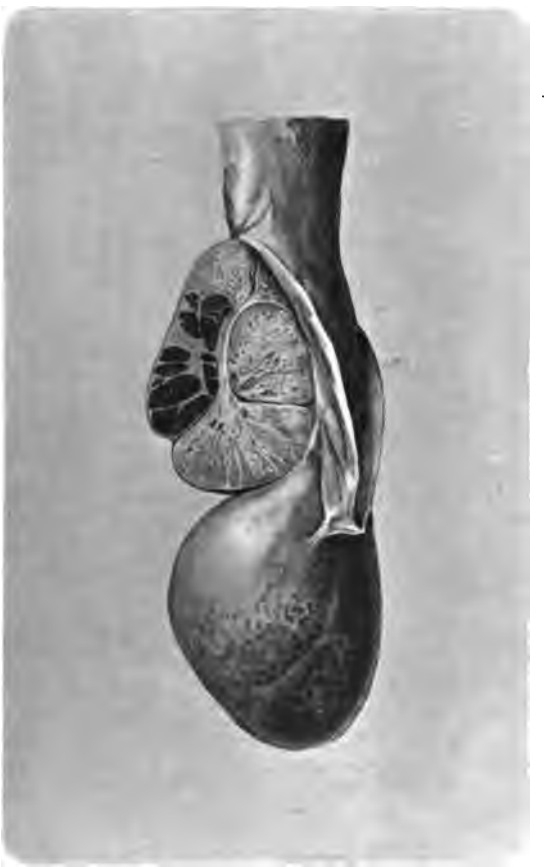
Spangaro ('Lo Sperimentale,' an. 57, F. 3, 'Brit. Med. Journ.' Epitome) found spermatozoa in the testicles of three men aged 70, 64, and 69, on whom respectively vasectomy had been performed twelve days, six months, and two and a half years previously.[1]

If further proof of spermatogenesis in the testis after section of the vas were needed, this has been supplied in the sheep and

[1] I have had the opportunity of examining the state of the testes after vasectomy on several occasions, and after considerable intervals, and have in most cases found no diminution in the size of the organs. Dr. A. H. Greg informs me that he has found the testis perfectly normal four years after the accidental section of the vas in a radical cure for hernia.

FIG. 10.

Specimen No. 36A, Royal College of Surgeons. The testicle of a Southdown sheep on which when a lamb double vasectomy was carried out, the vas deferens being divided between two ligatures. In consequence of some interference with the blood supply complicating or following the operation, the testicle has undergone a remarkable degree of atrophy. The operation was carried out March 3rd, 1902; on June 27th the right



testicle was found to be quite small, consisting of a lower mass about the size of a filbert (lower end of epididymis) and an upper of the same dimensions. The vertical diameter of the entire organ, including the epididymis, is only 70 mm., and that of the body of the testicle alone 28 mm. The extreme vertical measurement of the left organ, which attained the full size, was 100 mm., that of the body of the testicle being 80 mm. The animal was killed slightly over a year after the operation. [Natural size.]

fowl by Shattock and Seligmann in their communication to the Royal Society, vol. lxxiii.[1]

It is therefore a perfectly demonstrated fact that in man and animals the growth of the testicle and its function of producing spermatozoa is independent of the integrity of its vas. It is also an interesting fact that retention of the secretion does not produce a dilatation of the tubules, though there is usually some distension of the epididymis.

In proposing vasectomy as a substitute for castration the ensuing line of argument appears to have been followed:

1. Division of the vas in an operation for the cure of varicocele was followed by atrophy of the testis.

2. Atrophy of the testis would in its effects be similar to castration.

3. Castration produces atrophy of the prostate.

4. Therefore section of the vasa will cause atrophy of the prostate.

A mistake was made in attributing to vasectomy an effect on the testis which was really due to interference with its blood supply.

Fig. 10, which represents a specimen furnished by the work of Shattock and Seligmann, shows the truth of this statement.

White recognised the fact that section of the vas did not affect the testis, and performed experiments to determine if section of the vas produced any effect on the prostate, although it had no effect on the testis. The results of his experiments are given below.

Results of vasectomy in the dog (*White*, 1895).

No.	Interval between vasectomy and death.	Weight of prostate after vasectomy in grammes.	Loss of weight of prostate in grammes.	Weight of dog in kilos.
19	8 days	9·070	0·00	10·85
17	10 „	4·31	4·56	10·23
20	25 „	6·63	6·37	15·41
6	33 „	2·48	10·52	13·60
7	37 „	1·01	4·65	9·97
16	52 „	4·35	14·65	22·22
18	52 „	7·45	11·65	19·30

(According to White the weight of the normal prostate in the dog measured in grammes equals the body weight measured in kilos.)

[1] "Observations upon the Acquirement of Secondary Sexual Characters indicating the Formation of an Internal Secretion by the Testicle."

It is to be noted that a very material loss of weight was found after an interval of ten days, amounting to nearly half the normal weight. If these results are compared with White's experiments on the effects of castration it will be seen that as regards the loss of weight of the prostate they are very similar.

Guyon in the 'Ninth Surgical Congress' in 1895 published his results of vasectomy in dogs. Four experiments were performed, the interval between the vasectomy and the examination of the prostate being respectively five months, four months, two and a half months, and two and a half months. In no case was there any loss of the bulk of the prostate.

Except in the last case, when some atrophy of gland tissue was noted, the only change found was some condensation of the stroma round the gland lobules. It should be noted that the atrophy of gland tissue occurred in one of the experiments in which only two and a half months elapsed between the double vasectomy and the examination, and not after the longer interval. It was further observed that, when castration on one side and vasectomy on the other were performed, no change in the prostate occurred. These results are in striking contrast with those of White in that no loss of bulk of prostate was noted in any case. With the object of deciding between the results of White and Guyon, the experiments set forth below were performed by the author of this paper.

Results of vasectomy in the dog and cat (Author).

In Table I there are seven experiments. In six cases the testes were examined microscopically, and in three instances spermatogenesis was found in active progress, while in the remainder the production of spermatozoa was absent although the tubules were of full size.[1] The entire organs were not examined in serial sections, and it is therefore impossible to exclude the presence of spermatogenesis. In addition it cannot be stated that this had not taken place or would not have occurred if the animal had lived.

The reason for the absence of spermatogenesis cannot be stated, but it is possible that it may be attributed to some injury to the structures of the cord during the operation of vasectomy,

[1] In Case No. 12 it is to be noted that spermatozoa were present in the epididymis, though absent from the tubules of the testis.

TABLE I.

No.	Animal.	Time between operation and death.	State of testes.	State of prostate.
0	Adult dog.	11 months.	Spermatogenesis in progress.	Normal, both macro- and microscopically.
3	Puppy.	6 months.	Spermatogenesis in progress.	Weight 2980 grammes; normal, both macro- and microscopically.
5	Puppy.	11 months.	Full size; tubules well developed; no spermatogenesis.	Normal in shape and bulk (preserved intact).
12	Puppy.	12 months.	Full size; tubules of normal calibre; cells almost limited to a peripheral layer; no spermatogenesis; the tubule of the epididymis distended with dense masses of spermatozoa.	Normal in shape and bulk; dog weighed 5·7 kilos; prostate weight, 1·82 grammes; normal under the microscope.
13	Dog.	5 months.	Full size; spermatogenesis in active progress.	Normal in shape and bulk (preserved intact).
14	Dog.	8 months.	Full size; spermatogenesis doubtful.	Normal in shape and bulk; normal under microscope.
11	Kitten.	6 months.	Full size; tubules normal in size, but contained no spermatoblasts.	Normal macro- and microscopically; normal in shape and bulk.

such as interference with the blood-vessels insufficient to produce atrophy of the testis as a whole (*vide* Exp. 6, Table III). In spite of the absence of spermatogenesis the testes were of full size and of normal appearance.

It will be seen that the results obtained are wholly at variance with those of White, but agree very nearly with those of Guyon. In no instance was atrophy of the prostate found; the organ was normal to the naked eye in every case, and presented no abnormality under the microscope in the five cases which were submitted to this form of examination. In forming a naked-eye estimate as to the normal condition of the organ which was the subject of experiment, it was compared in form, bulk, and area of cross section with the organ of a dog of the same age, breed, and size, and also with an organ that was atrophied as the result of castration. When weight was taken as a criterion no departure from the normal was found, when judged by the relation found to exist (in the type of dog submitted to experi-

ment) between the weight of the body and that of the prostate. The relation between the weight of the body and of the prostate of the dogs examined for the purposes of this investigation does not at all tally with the relation quoted by White. In order to establish a relation between the weight of the prostate and the body weight of a dog, White examined thirty dogs, and the relation thus established was used in calculating the loss of

FIG. 11.

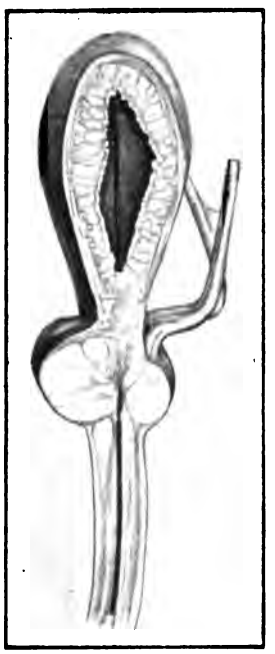


FIG. 12.

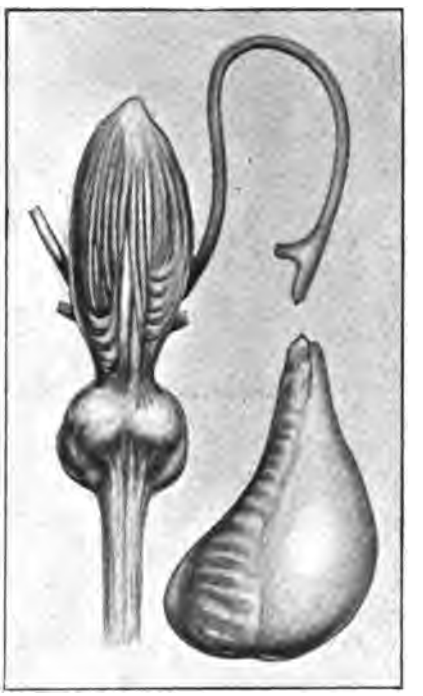


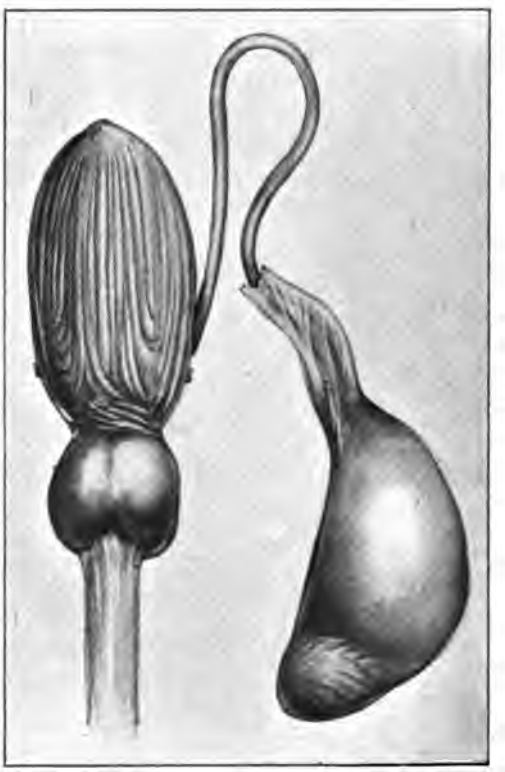
FIG. 11.—Vertical section of bladder and prostate of a dog on which double vasectomy was carried out eight months before the animal was killed. It shows that no atrophy of the prostate has taken place. The testicles grew to their full size. (No. 14 in Table.)

FIG. 12.—The bladder, prostate, and one testis of a dog on which double vasectomy was performed five months before the animal was killed. It shows that no atrophy has taken place either in prostate or testes, which have grown to their full size. Spermatogenesis was in active progress in the tubuli. (No. 13 in Table.)

weight after castration or vasectomy. Thus, a dog of sixteen kilos was castrated and after a particular interval was killed and the weight of its prostate ascertained. This weight was then subtracted from the computed weight, and the difference was

used to represent the loss of weight due to castration or vasectomy respectively. The accuracy of White's experiments therefore rest on the correctness of the relation that was found to exist between the weight of a dog's prostate and that of its body. The dogs used by myself were of the fox terrier type, while those used by White were of a much larger size. Dogs of the

FIG. 13.



The bladder, prostate, and testis of a normal dog of the fox terrier breed. The weight of this dog was about the same as that of the dogs the subject of the foregoing experiments (Figs. 11 and 12).

same weight as used by White were therefore obtained, and the relation between their body weight and that of their prostate was noted. Even here the discrepancy is very great; thus, in the case of a collie dog, whose body weight was 16 kilos, the prostate weighed only 7·6 grammes, and in another collie dog which weighed 30 kilos the prostate only weighed 20 grammes, whereas, according to White, they ought to have weighed 16

and 30 grammes respectively. It therefore seems probable that some error has crept into White's figures when computing the relation between the body and prostate weight in the American dogs. If the computed weights are wrong then the vasectomy experiments of White are valueless, and much doubt must also rest on the rapid atrophies noted in the prostate in cases of experimental castration.

The experimental evidence as regards the effect on the normal adult prostate in animals may therefore be summarised as follows:

(1) Double vasectomy has no effect on the testes or the prostate.

(2) Double castration causes an atrophy of the prostate. The evidence as to the time required to effect this is incomplete. It is possible that it varies with different animals.

It will be now necessary to turn to the evidence to be gleaned on this subject from clinical and pathological observations.

Clinical and pathological observations on the results of vasectomy.

There is practically no evidence as to the effect of vasectomy on the normal human prostate; arguing from experimental evidence, no effect would be expected. In the case of prostatic enlargement the evidence is scanty, but there is sufficient to show that vasectomy is not followed by an atrophy of the enlarged gland. The following are the cases which I can find, in which a reliable statement useful for the purpose has been made as to the state of the prostate when occasion offered for an examination either in the *post-mortem* room or at a supra-pubic cystotomy.

(C. W. Frank, 'Lancet,' September, 1897.)

Male, aged 70 years. Enlarged prostate; acute cystitis; double vasectomy; urination improved; prostate decreased in size; death. Necropsy showed prostate to be converted into "a bag of pus."

(Lunn, 'Clin. Soc. Trans.,' 1899.)

E. S—, male, aged 76 years. Admitted in Marylebone Infirmary January, 1898, for retention; prostate as large as a tangerine orange; micturition up to twenty-four times in the twenty-four hours. April: left vasectomy, no improvement; June: right vasectomy, no further retention. Died in December of carcinoma of the liver. Specimen in the Royal College

of Surgeons Museum (No. 4315A). Description as follows: "Lateral lobes considerably and uniformly enlarged, organ measuring $2\frac{1}{8}$ inches from side to side, and being proportionately enlarged in all directions. Vesiculæ seminales and proximal ends of vasa deferentia presented no abnormality." A section taken from the posterior part of the organ showed considerable gland tissue.

(A. C. Wood, 'Annals of Surgery,' 1900.)

W. L., aged 69 years. Increased frequency of micturition, 10 years; vasectomy, no improvement; catheter still required; death. Autopsy revealed carcinoma of prostate.

(Woodarz, 'Zeitschrift für Pract Aertze,' 1898.)

Death after four months. Neither testes nor prostate showed any change; no fatty change in prostatic epithelium.

R. Harrison ('Lancet,' May 5th, 1900) states that he has examined the enlarged prostate after one double castration and five double vasectomies. The examinations were made in two cases after death and in four cases during a supra-pubic cystotomy. In all he found "shrinkage" of the enlarged prostate. Details are not sufficient to allow any certain conclusions being drawn; moreover, there are no data given as to the condition of the testes in the cases of vasectomy, but it is significant that in no case had normal micturition been established. This evidence is meagre, but where a scientific investigation has been made there is no evidence that vasectomy produces an atrophy of the enlarged prostate.

Clinical and pathological observations on the results of castration.

Although castration in adult animals produces an atrophy of the normal prostate, and although it cannot be denied that an appreciable diminution in size of the diseased organ, with an accompanying amelioration of the clinical symptoms, may, after an appreciable interval, follow castration, there is definite evidence to show that castration may fail to produce any marked diminution in size of the enlarged organ.

The following cases may be quoted in this connection.

The intervals between the castration and examination of the prostate vary from two days to sixteen months.

J. W. White has published a case in which the prostate was

examined two days after double castration. Microscopical examination is stated to have shown proliferation of the epithelium and of the connective tissue. This is attributed to commencing atrophy of the organ. The appearances on which this statement is founded seem to be those which are found in any enlarged prostate, and are partly due, it is believed, to inflammatory changes and partly due to the section passing obliquely across the alveoli. It should be borne in mind that even White in his experiments on dogs found no change before the eighth day, so that his own observations would indicate that the diseased human prostate undergoes a more rapid atrophy than that which occurs in the normal prostate of the dog. (*Interval two days.*)

(Mansell Moullin, 'Clin. Soc. Trans.,' 1895.)

Male, aged 64 years. Double castration; death in eleven days. At the *post-mortem* examination all parts of the gland were uniformly enlarged. Projecting from one of the lateral lobes was an out-growth which was soft, flabby, disc-shaped, and covered by a wrinkled mucous membrane. This wrinkling was attributed to a shrinking of the tumour. Microscopical examination showed the usual appearances of an enlarged prostate. (*Interval eleven days.*)

(Griffiths, 'Brit. Med. Journ.,' 1895.)

Male, aged 74 years. Double castration; death in eighteen days. Prostate not markedly diminished. Microscopical examination showed fatty change in the epithelium, proliferation of the cubical cells. Increase of new connective-tissue cells at the expense of the muscle and mature connective tissue. The changes are said to resemble those seen in dogs shortly after castration. The plates published with the paper show appearances which the author believes are common to all enlarged prostates. (*Interval eighteen days.*)

(C. B. Kelsey, 'New York Medical Record,' May 23rd, 1896.)

Male; castrated for enlarged prostate; no improvement; died in five weeks. At the *post-mortem* examination the prostate weighed 45 grammes. Surface nodular. Proportion of elements were normal under the microscope. The epithelial cells were large, clear, and distinct. There was no proliferation. There were a few fat droplets in some of the epithelial cells. No signs of atrophic change with this exception. (*Interval five weeks.*)

(Davies-Colley, 'Path. Soc. Trans.,' February 4th, 1896.)

Male, aged 73 years. Suffered from prostatic symptoms for four years. Urine was passed eight times in the night. The prostate *per rectum* measured 2½ inches in breadth and 2 inches in other directions.

April, 1895: Double castration. Much improvement in one month; the urine was passed only three times in the night. The prostate remained the same size.

In December, 1895, the man died of bronchitis and pyelitis. Bladder fasciculated. Right lobe pushed the urethra to the left. Trigone also pushed forward. The external measurements of the organ were the same as before. There was no microscopical examination. (*Interval eight months.*)

(C. M. Nichol, 'Ann. of Surg.,' 1898.)

J. S. B—, aged 64 years, suffered for some years from enlarged prostate. There was great increase in the gland as shown by rectal examination. There was cystitis and residual urine to the extent of 12 ounces. Double castration was performed on April 17th, 1896.

In May of the following year, the prostate was as large as ever, and could be felt through the anterior belly-wall. Supra-pubic prostatectomy was performed, and a 7-ounce tumour shelled out. The patient recovered, but never regained proper control. Malignant disease is excluded by the fact that the patient was alive and well a year after the operation, although he had not regained control. (*Interval thirteen months.*)

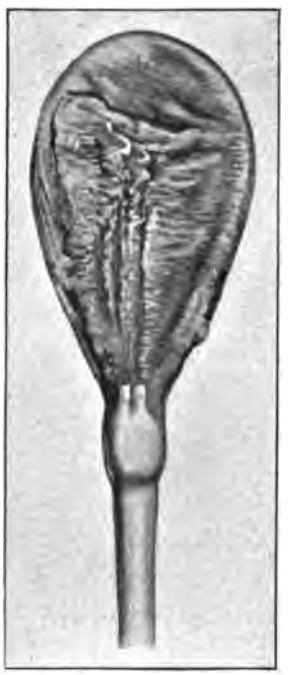
(J. R. Lunn, 'Clin. Soc. Trans.,' vol. xxxii., Specimen 4315B, Royal College of Surgeons Museum.)

E. H—, male, aged 72 years. Admitted passing his urine 20 to 24 times in the twenty-four hours. Left vasectomy in May, 1896. No improvement. Castration on the right side, August, 1896. Some improvement, but retention at times. Castration on the left side August, 1896. The prostate was then noted to become less prominent on the right side than on the left. Micturition was reduced to 10 times in the twenty-four hours. Died December, 1897. *Description of specimen:* "The gland is uniformly and considerably enlarged, its transverse diameter amounting to 2⅛ inches from side to side. (*Interval sixteen months.*)

The cases where there was a long interval between castration and the examination of the enlarged prostate show unmistak-

ably that castration cannot be relied on to produce an atrophy of the diseased organ. In those cases with a shorter interval the statements are somewhat contradictory. Mansell Moullin found no change microscopically, whereas both White and Griffiths described marked alteration. They both ascribed to the effects of castration appearances which are found, according to my experience, in all enlarged prostates. There was a tendency, no doubt, when castration was first introduced, to

FIG. 14.



Hypoplasia of prostate in puppy eleven months after double castration (No. 4, Table II).

attribute any improvement in micturition to the operation; the fact that simple rest in bed had, in many cases, resulted in as striking an amelioration was neglected. The improvement in clinical symptoms made observers expect and, therefore, prone to see corresponding pathological changes in the organ under consideration. On the other hand, it is very difficult to explain away such an observation as that published by Mansell Moullin, in which, at the end of three weeks, the prostate, formerly large, was represented merely by a fusiform thickening.

Some observers, recognising that the sudden improvement could not be due to a commencing atrophy of the organ, have offered other explanations, such as decrease in vascularity, improved muscle tone, or even relaxation of the vesical sphincter. In the case of the normal organ, if we exclude White's experiments, observations seem to point to a very appreciable time being necessary before any striking decrease in size takes place. Guyon found well-marked atrophy after five months, but he says that shrinkage was only well established after two and a half months.

In my own experiments on cats there was practically no change in six months, but in the case of a puppy there was extreme hypoplasia in eleven months.

Effects of castration (Author).—TABLE II.

No.	Animal.	Time between operation and death.	State of prostate.	State of vasa.
4	Puppy.	11 months.	Markedly hypoplastic.	Vasa very small.
8	Cat (adult).	6 months.	Normal.	
9	Cat (adult).	6 months.	Normal.	

The effects on the prostate of unilateral castration.

Many clinical observers have tried to trace a dependence of one side of the prostrate on the integrity of the testis of the same side and a one-sided shrinkage of the organ is stated to have followed castration on the same side. The evidence of this, as far as I can find, is entirely clinical and does not rest on satisfactory *post-mortem* examination. Guyon found no alteration in the prostate of dogs on whom castration on one side and vasectomy on the other had been performed. This evidence is corroborated by Experiment 6, Table III. In this case the vessels of both cords were tied, with the exception of the small vessels on the vasa deferentia. Atrophy of one testis followed, but the opposite testis, though presenting no spermatogenesis, was found to have well-developed tubules with well-marked lumina. The vessels on the vas were large and distended with blood and had evidently by their increase in size saved the testis from atrophy. The prostate was

normal in every way. In the experiment of Sir Astley Cooper, in which the vas of one testicle was ligatured, and the other testicle sloughed after ligation of its vessels, the prostate is of full size, and quite symmetrical, although the dog was allowed to live four years afterwards (Spec. No. 4289, Royal Coll. Surg. Museum).

The occurrence of a normal prostate with only one testis and that not producing spermatozoa (see also Table I) is interesting and raises the point as to whether such a testis can provide an internal secretion able to influence the secondary sexual characters and sexual apparatus, or whether, as would appear from the researches of Shattock and Seligmann, this testis had at one time produced spermatozoa.

Effects of ligation of the vessels of the spermatic cord.

That ligation of all the vessels of the cord causes an atrophy of the testis there can be no doubt. In the case of partial ligature Griffiths has shown that the results vary with age and the vessels ligated. From the imperfect recognition of this fact arose the error of attributing to section of the vas an atrophy of the testis that was due to the cutting off of its blood supply. The young testis is much more liable to resent any interference with its blood supply than is the adult organ. This fact has a very practical application when operations for the radical cure of hernia are undertaken in those of tender years.

Again, it must not be forgotten that actual section of the vessels is not the only way in which the blood may be cut off from its distribution. A thrombosis may effect the same result, and this, though most likely to follow an infection of the wound, may apparently occur in a clean wound. It is probable that thrombosis of the spermatic plexus accounts for some discrepancies in the observations on the testis and prostate after vasectomy.

From what the writer has seen he believes that the operation for varicocele is to-day undertaken with too little appreciation of the possible effects on the testis, and would urge that care be taken not to include all the veins in the ligature.

The occurrence of orchitis and of hydrocele even after the modern high operation for varicocele, indicates with sufficient clearness some serious interference with circulation of the testis.

An inquiry into the histories, as regards the power to pro-

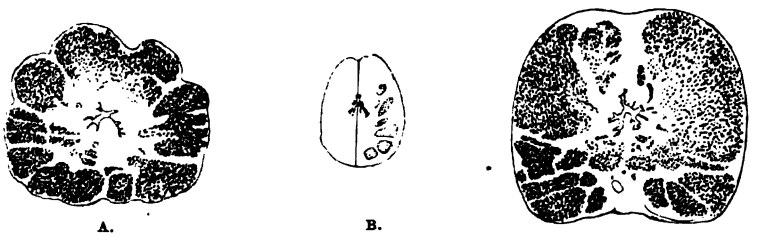
create children, of cases of bilateral operation for the cure of varicocele might afford some interesting statistics.

Effects of ligation of vessels of spermatic cord (Author).—TABLE III.

No.	Animal.	Time between operation and death.	State of testis.	State of prostate.
7	Dog (adult).	5 months.	Atrophic.	Small, tough, and atrophic; weight 4 milligrammes; weight of dog 7 kilos; microscopically it consisted of fibro-muscular tissue; gland tissue is reduced to narrow tortuous columns with little or no lumen.
6	Puppy.	5 months.	Left, atrophic; right, smaller than normal; no spermatogenesis; cells show karyokinetic figures; lumen well marked; cells long; some small vessels had escaped ligation and were distended with blood.	Normal, macro- and microscopically; weight 1·62 grammes; weight of dog 5·8 kilos.

I may illustrate these conclusions histologically, in so far as the prostate is concerned, by the following figures:

FIG. 15.



A. B. C.

(A. Normal prostate. B. Atrophic prostate. C. Prostate after a double vasectomy.) All the figures are drawn to the same scale. The sections are taken at right angles to the urethra and magnified two diameters. If C is compared with A it will be seen that vasectomy has produced no change at all either in respect to size or the presence and distribution of gland tissue. On the other hand, if B is compared with A it will be seen that extreme atrophy has followed the ligation of the vessels of the spermatic cords. The gland tissue is only faintly made out in this specimen. For microscopic appearances of A, B, C, see Figs. 16, 18, 17.

CONCLUSIONS.

(1) That the growth of the testis is independent of the integrity of the vas.

(2) That spermatogenesis is independent of the integrity of the vas.

(3) That the development, growth, and nutrition of the prostate are dependent on the presence of the testes, and independent of the integrity of the excretory ducts of those organs.

FIG. 16.

A microscopic section of the normal prostate of the adult dog, A, in the preceding figure.

(4) That, in addition, the presence of one testis, even if the excretory duct has been divided, is sufficient for the perfect growth and nutrition of the prostate.

(5) That castration in youth produces an atrophy of the prostate.

(6) That castration in adult life produces an atrophy of the prostate.

(7) That such an atrophy takes an appreciable time to become established.

(8) That castration, although it produces an atrophy of the normal prostate in the course of time, is not to be depended upon to produce an appreciable atrophy useful for the treatment of the enlarged organ.

Practical application of the foregoing conclusions.

(1) That a single or double vasectomy is useless as a means of producing prostatic atrophy.

(2) That since castration cannot be relied on to produce an appreciable atrophy of the enlarged prostate, it should be abandoned as a means of treating such disease.

(3) That treatment of the enlarged prostate must in future consist of some form of prostatectomy as a radical, and of cleanly catheterisation as a palliative, measure.

CATALOGUE OF THE AUTHOR'S EXPERIMENTS.

Vasectomy.

Experiment O.—Rough-haired Irish terrier, adult. December, 1901—Double vasectomy and ligature. Vessels intact. November 25th, 1902—Killed. Ligature found effective. Interval eleven months. Testes normal to the naked eye. Epididymis dilated with seminal fluid. Microscope—Tubules normal; spermatogenesis in progress. Cells showed mitotic figures. Prostate normal, both macro- and microscopically. Gland, fibrous, and muscular tissue in normal proportions. This dog showed distinct sexual desire after the vasectomy.

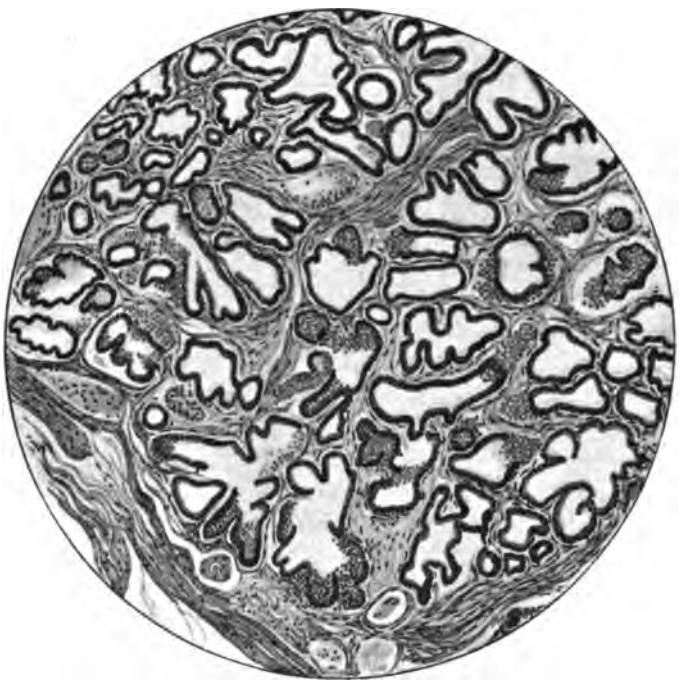
Experiment III.—Rough-haired puppy. Six weeks old. February, 1902—Double vasectomy and ligature. Vessels intact. August, 1902—Killed. Operation found effective. Interval, six months. Testes, normal. Spermatogenesis in progress. Prostate, weight 2·980 grammes. Normal both macro- and microscopically. Gland, fibrous and muscular tissue in proper proportions. Surface showed distinct indications of division into lobules.

Experiment V.—Puppy. November, 1902.—Double vasectomy and ligature. October, 1903—Killed. Ligature found effective. Interval eleven months. Testes normal in size. Tubules full size and filled with epithelium. No spermatogenesis. Tissue gene-

rally healthy. Interstitial cells normal. Prostate normal in bulk and shape. Microscopical sections not made. Specimen preserved entire.

Experiment XII.—Puppy, half grown. May, 1903—Double vasectomy (some injury to veins on left side). May, 1904—Killed. Operation found effective. Interval, twelve months.

FIG. 17.



(Experiment XII.) A microscopic section of the prostate of a dog, aged 13 months, upon which the operation of double vasectomy was performed when a puppy (c, in Fig. 15). Weight of the dog was 5·7 kilos., and that of the prostate 1·82 grammes. Glandular, fibrous, and muscular tissue are present in normal proportions. The size and shape of the glandular alveoli as well as the epithelium are normal. The crowding of the epithelial cells seen in some of the alveoli is due to the section passing through the extremity of those particular glands. If comparison is made with Fig. 16 it will be seen that there is no indication of any departure from the normal. The testes were of the usual size and shape for a dog of the fox terrier type.

Testes normal in size and shape. No spermatogenesis present, but the tubule of the epididymis is distended with dense masses of spermatozoa. Prostate normal in bulk and form. Weight,

1·82 grammes. Microscopically, epithelium normal. Gland, fibrous, and muscular tissue in normal proportions. Weight of dog, 5·7 kilos.

Experiment XIII.—Long-haired fox terrier, adult. May, 1903—Double vasectomy (vessels on vasa left intact). October, 1903—Killed. Ligature found effective. Interval, five months. Testes, full size. Spermatogenesis in active progress. Prostate normal in size and bulk. Specimen preserved entire for Royal College of Surgeons Museum.

Experiment XIV.—Long-haired fox terrier, adult. May, 1903—Double vasectomy (vessels on vasa not tied). January, 1904—Killed. Ligature found effective. Interval, eight months. Testes, full size. Epididymis large and distinct. Tubules well formed. Spermatogenesis doubtful. Prostate. Sagittal section made of preparation. Prostate normal in bulk and shape. Microscopically, epithelium normal. Gland fibrous, and muscular tissue in normal proportions. Specimen in St. Thomas' Hospital Museum.

Experiment XI.—Kitten, about twelve weeks old. March, 1903—Double vasectomy. Vessels left intact. September, 1903—Killed. Interval, six months. Testes, organs full size. Microscopically—Tubules normal size. No spermatoblasts. Lumen of tubules in varying degree filled with cells and coarsely vacuolated material resulting, apparently from the escape of epithelial elements (*cf.* testis, Experiment VI). On neither side were there any spermatozoa in the epididymis. Groups of interstitial cells present. Prostate, quite normal microscopically.

Castration.

Experiment IV.—Black and tan fox terrier, eight weeks old. November, 1902—Double castration. October, 1903—Killed. Interval, eleven months. Vasa deferentia very small. Prostate small and atrophic, and only represented by a slight bulbous enlargement. Specimen preserved intact in St. Thomas' Hospital Museum.

Experiment IX.—Tom cat, almost adult. March, 1903—Double castration. September, 1903—Killed. Interval, six months. Prostate showed no signs of atrophy.

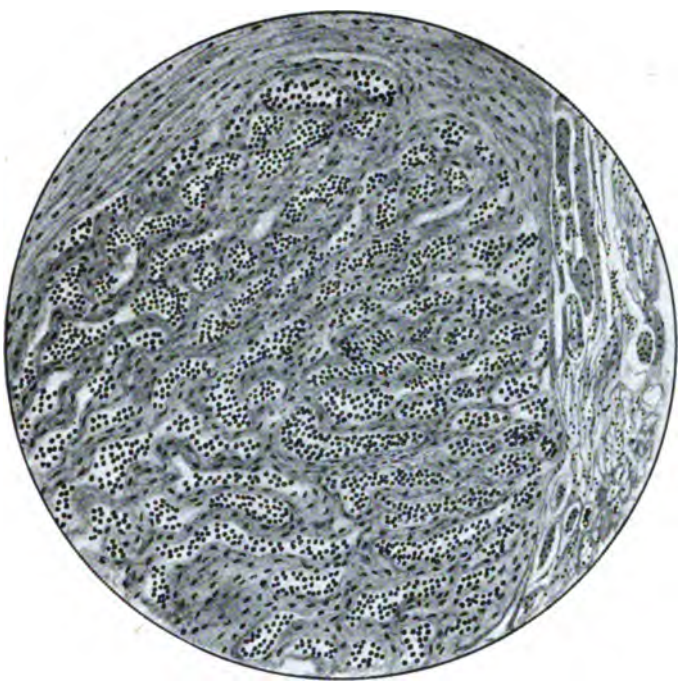
Experiment VIII.—Black and white Tom cat, adult. March 11th, 1903—Double castration September 27th, 1903—Killed.

Interval, six months. Prostate, gland tissue, and alveoli normal.

Ligation of vessels.

Experiment VII.—Smooth-haired brown and white carriage dog, adult. December 3rd, 1902—Vessels of cord tied on both sides. February 17th, 1903—Testes atrophied. May 13th, 1903

FIG. 18.



(Experiment VII.) A microscopic section of the prostate of a dog, the vessels of whose spermatic cords were tied five months previously (B in Fig. 15). Both vasa deferentia were intact. The organ was entirely atrophied, and appeared as a tough, fibrous, fusiform thickening on the urethra. Both testes completely atrophied, and under the microscope showed no signs of glandular tissue. The specimen represents the effect of the interruption of its blood supply on the testis. It can be seen that the remains of the glandular tissue of the prostate presents itself as narrow tortuous channels with little or no lumen.

—Dog killed. Interval, five months. Ligature found effective on both sides. Vessels below ligature empty. Vasa intact on both sides. Testis, right small, atrophic, and soft. Microscopically, the body of testis was represented by a fibrous nodule,

without trace of tubules. Left presented the same appearance as the right side. Prostate small, atrophic, and tough. Microscopically it consists of fibro-muscular tissue. The gland tissue distributed through this presents itself as narrow, tortuous columns, with little or no lumen. Weight of dog, 7 kilogrammes. Weight of prostate, 4 milligrammes.

Experiment VI.—White rough-haired fox terrier, eight weeks old. December, 1902—All vessels in the cords tied with the exception of the small vessels on the vasa. February, 1903—Left testis small and atrophic. Right testis smaller than normal, but not atrophic. May, 1903—Dog killed. Interval, five months. Testes—left, small, soft, and quite atrophied. All the vessels beyond the ligature were empty. Vasa very small. Testes—Right, somewhat smaller than normal. The veins of the pampiniform plexus were completely interrupted at the seat of ligature. The small vessels which had been left untied on the vas were of larger size than normal, and distended with blood. The vas was of full size. Microscopically the tubules were full size. Cells showed karyokinetic figures. No spermatogenesis in progress. Judging from the size of the tubules, it was possible to believe that spermatogenesis had taken place, and the contents to have been passed forwards. The lumen of the tubules was free, and the cells long. Compare state of testis and epididymis in Experiment XII, Table I. Prostate normal in size, and also both macro- and microscopically. Weight of dog, 5·8 kilogrammes. Weight of prostate, 1·63 grammes.

My best thanks are due to Mr. S. G. Shattock and Mr. C. G. Seligmann for much help and useful suggestion.

October 18th, 1904.

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7. *An unusual form of consolidation of left lung occurring in a case of occlusion of bronchus by blood-clot.*

By T. J. Horder.

Before describing the specimen exhibited this evening, I will refer very briefly to the clinical history of the case. A gardener, aged 32 years, complained of a "wheezy" cough about the beginning of July, 1903. He continued at work until July 13th, when suddenly, whilst out walking, he came over very cold, had

sharp pain in the chest, coughed violently, and was very short of breath. In this condition he was taken home. Thinking it another attack of ague, from which he had suffered whilst living in India seven years previously, he went to bed and in three or four hours felt much better. He was seen by a doctor two days later, and was admitted to the Great Northern Hospital on July 20th, a week after his attack. The patient gave a history of having had syphilis thirteen years previously. When first examined, his temperature was found to be 101·8°, his pulse 108, his respirations 32. Neither the dyspnœa nor the pain was

FIG. 19.

Section of *right* lung, showing recently inhaled blood in the alveoli. Beyond this, and emphysema, the lung is natural in appearance. (× 230.)

marked. There was slight cyanosis. The chief symptom was the cough, occurring in paroxysms, and resulting in but little sputum, composed of thick mucus, at times blood-tinged. The cough was so troublesome that opium was needed to relieve it. The patient did not look very ill. Examination of the heart and abdominal viscera gave no abnormal signs. The right lung seemed quite healthy. The left lung gave signs of greatly diminished function; the left side of the chest moved badly, the vocal vibrations were diminished, the percussion note was markedly impaired, especially behind and in the axilla, and the breath-sounds were very feeble. These signs becoming still

more marked, the left side of the chest was explored fourteen days after admission, with a negative result. The exploration was repeated in two places three days later, and a fourth time, in the front of the chest, a week afterwards. The result was still negative. The scanty sputum was examined on three occasions for tubercle bacilli, but none were found. Repeated examinations of blood-films were also negative as regards the malarial parasite. A month after admission the whole of the

FIG. 20.

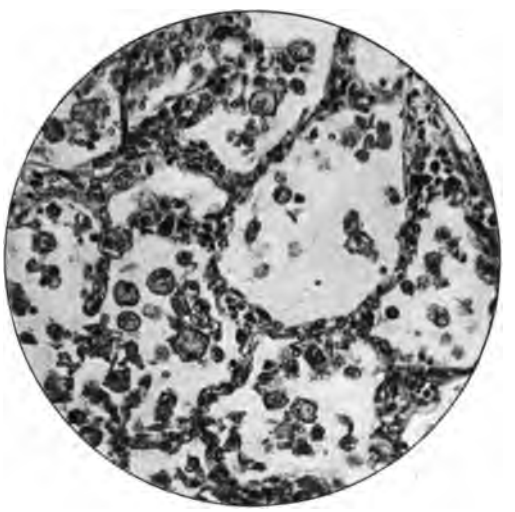
Section of *left* lung, including pleural surface. At the upper part of the section the pleura is seen to be greatly thickened by fibrous tissue. The lung is similarly affected. (× 230.)

left side of the chest was dull to percussion, and, apart from a little distant bronchial breathing occasionally heard near the spine of the scapula, the left lung was everywhere dull to auscultation. The temperature had risen soon after admission to 103·4°, and during the third and fourth weeks rigors occurred, the temperature twice reaching 105°. By the end of the fourth week there was a regular quotidian intermittent fever, ranging from 97° to 103·4°, which lasted throughout the rest of the illness. A month after admission a blood-count resulted in 5,650,000 red cells and 24,000 leucocytes. There were no signs of aneurysm (other than the condition of the left lung), and no evidence of arterial degeneration. No change occurred in the physical signs, but the dyspnœa and the cough abated considerably. On

September 8th, seven weeks after admission, eight weeks after the attack of dyspnœa, and about ten weeks after the beginning of his illness, the patient had a sudden, very profuse hæmoptysis and died.

At the *post-mortem* examination the only pathological organs were those seen in the specimen. The right lung (not shown) was somewhat emphysematous, and, on section, showed patches of recently inhaled blood; otherwise, it was natural (Fig. 19).

FIG. 21.



Section of *left* lung, at a part not showing the thickened trabeculæ. The alveolar walls are well marked, and in the alveoli are seen large (?) endothelial cells and small plasma cells. (× 500.)

Microscopic examination shows the alveoli filled by blood-cells, none of which have undergone ingestion by the lung-cells. The left lung was firmly adherent to the thoracic wall, to the pericardium, and to the diaphragm. The visceral pleura was much thickened, especially over the posterior and pericardial aspects, where it attained a thickness of an eighth of an inch. The lung was everywhere quite solid, sinking in water; the division into lobes was in great part lost. Section showed a uniform surface, ashy-grey in colour, dry, firm, and slightly granular. The bronchi contained neither pus nor blood; their walls were thickened. On close inspection the trabeculæ were seen to be also thickened. Microscopic examination shows a large increase

in the pleural, peribronchial and interalveolar connective tissue, most of the new tissue being young (Fig. 20). The alveolar septa are thick, and, in places, the cells lining them are cubical. In the portions of the lung not invaded by the new fibrous tissue, the alveoli are filled in part by large round cells, evidently proliferated endothelial cells, many of which are without nuclei and vacuolated, and in part by smaller cells which react well with Pappenheim's stain, and are therefore, presumably, plasma cells

FIG. 22.

Transverse section of aorta. The inner coat is greatly thickened, but without any evidence of degeneration in the new tissue. The middle coat is little altered, but here and there it shows small ruptures. The appearance is highly suggestive of syphilitic aortitis. (× 230.)

(Fig. 21). There is a notable absence of erythrocytes and of leucocytes. Orcein stained sections show, if anything, a diminution of elastic elements. Weigert's stain shows no fibrin, but a few micro-organisms uniformly distributed in the alveoli, and chiefly cocci. A gland at the bifurcation of the trachea, nearly two inches long and much indurated, shows nothing on section except the changes of chronic inflammation. The left bronchus was seen to be completely filled by a large egg-shaped blood-clot adherent to the wall of the tube, but softened at a small spot on its inner and posterior aspect. At this spot a probe was found to pass straight into the descending aorta. On dividing the clot vertically it was found to be soft at the centre. Micro-

scopically, it consists of laminated masses of fibrin and *débris*, and at the surface micro-organisms can be demonstrated in fair numbers. Detaching one half of the clot, the bronchus is found to be dilated in its whole length, its wall being much thinned in the direction of the aorta. Its surface is ulcerated, leaving the cartilages prominent. The recurrent laryngeal nerve is directly pressed upon. A section of the ulcerated bronchus shows loss of epithelium and inflammatory infiltration of subepithelial tissues. The aorta is diseased—the inner coat being considerably and irregularly thickened, but without any degenerative changes. The middle coat is deficient at several spots. The appearances are suggestive of syphilitic aortitis (Fig. 22). Opposite the clot in the bronchus there is a hole in the wall of the aorta a little smaller than a threepenny-piece, the edges of which are thick, smooth, and turned away from the aorta. This hole leads to a sac not bigger than a large pea, and this sac immediately communicates with the bronchus at the point of its greatest dilatation.

I interpret the sequence of events to have been as follows: The syphilitic disease of the aorta led to a small aneurysm which pressed upon the left bronchus, causing atrophy of its wall. The sac suddenly got free between the cartilages of the bronchial wall at the time of the patient's acute attack, and expanded within the lumen of the bronchus, to the inner surface of which it became adherent. The thinned sac, with its contained clot, becoming infected, gradually softened, leading to a slow septic absorption from the ulcerating surface of the bronchus which caused the leucocytosis and intermittent fever. Then came the fatal hæmoptysis.

The state of the lung and pleura is difficult of explanation and is the special point of pathological interest. The lung is not in a condition of pneumonia, either lobar or lobular. It is not collapsed. There is no evidence of tubercle or of syphilis. I think it must be explained as being due to the action of organisms of low virulence retained in the bronchi below the obstruction, upon lung tissue largely deprived of function. The only instance I can find of a pulmonary complication of aneurysm at all resembling this is one reported to La Société Médicale des Hôpitaux de Paris in November, 1901, by MM. Huchard and Bergouignan. The aneurysm was latent, and led to a clinical condition very similar

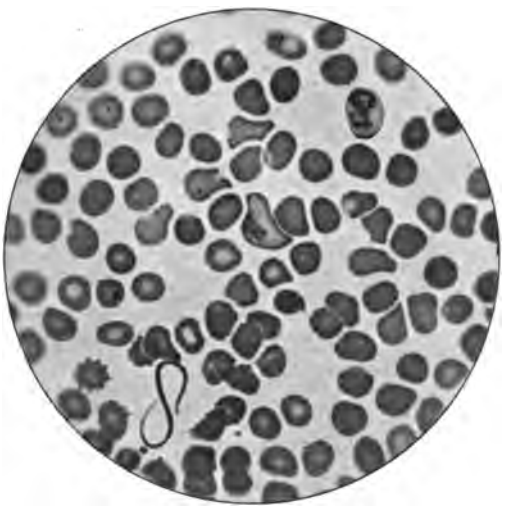
to the one here described. There were the signs of massive consolidation, the presence of "hectic" fever, several negative exploratory punctures were performed, and the termination was by hæmoptysis. The state of the lung *post mortem* seems to have been also very similar. Huchard cites the case as one of "massive pneumonia due to compression of the left vagus nerve." The vagus, however, though found to be much compressed, was not histologically examined. In my own case, also, the vagus is compressed, but examination by Marchi and Weigert-Pal methods fails to demonstrate any difference between the nerve-trunk above and below the seat of pressure. As the vagus trunk is normally somewhat ribbon-like in this situation, it is obvious that no amount of mere flattening of the nerve can safely be regarded as pathological. Huchard considers it to be sufficiently proved by the observations of Bignardi, Habershon, Hanot, Meunier, and others that pressure on the vagus nerve by lesions at this level favour infective processes in the left lung. If this be so, the condition must be regarded at present as purely functional, in the absence of any histological proof of degeneration of the nerve-fibres. In the case now under consideration the factor of vagus compression might well be present, and it is worthy of note that Babinski claims to have procured experimentally in rabbits similar lesions to those here described. *March 15th*, 1904.

8. *The simultaneous occurrence of filaria and malarial parasites in the blood.*

By C. F. Selous.

The slide shown is that of the blood of a man, aged 27 years, who was admitted into St. Thomas's Hospital suffering from a typical attack of malaria. The first onset of this disease occurred in India in 1899, and he has had numerous recurrences since at

Fig. 23.



The blood-film referred to in the text, showing the filaria near the bottom of the field, and two red corpuscles, each containing a malarial parasite; one corpuscle lies in the centre of the field, the other above and to the right. Leishman's stain, $\frac{1}{12}$ oil immersion.

intervals of a few months. He has never had symptoms of any kind pointing to filariasis. His spleen was found to be slightly enlarged, and his temperature chart is that of a tertian ague. There was no clinical evidence whatever of filariasis. The blood-film, which was taken at 9 p.m., was stained by Major Leishman's method and shows very numerous malarial parasites of the benign tertian type. At one spot, however, is a filaria, and under the same field of a $\frac{1}{12}$ inch objective can be shown, fortunately, two malarial parasites and the filaria. The discovery of the latter was made accidentally after the patient's discharge, so no search

could be made for further examples. Four other films, however, taken at the same time as the one exhibited, show no filariæ. There is no eosinophilia. This is, then, an example of the presence of these two parasites in the blood simultaneously. I have not been able to find, in the literature of the subject, any mention of this coincidental occurrence, though in monkeys the presence of trypanosomes and monkey malarial parasites together has been recorded. The occurrence is, therefore, perhaps not so common as one might naturally conclude it would be in those districts in which both organisms are indigenous. The simultaneous presence of these parasites might be of some importance clinically, seeing that the attacks of so-called "elephantoid fever" in filariasis appear to simulate ague very closely, and either disease might be falsely diagnosed as the cause of the pyrexial attack owing to the coincidental occurrence and discovery of its parasite.

November 1st, 1904.

Addendum.—Since the above was written I have learned that the concurrence noted has been once observed by Dr. D. Nabarro. Dr. Nabarro's observation is recorded in a report of the Sleeping Sickness Commission to the Royal Society, London, not yet published.

The patient was a native of Uganda, suffering from sleeping sickness; in his blood were found *Filaria perstans*, and a malarial parasite (probably the malignant or subtertian), together with trypanosoma.

In a second case the malarial parasite was found in conjunction with the trypanosoma alone in a Persian, the subject of sleeping sickness.

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9. *Acute lymphocythæmia.*

By Leonard S. Dudgeon.

[With Plate I.]

The case which I bring before this Society to-night is of great pathological interest, and serves to illustrate some very

important problems associated with this disease and also with the severe anæmias in general.

The history of the case is as follows:

Male, aged 37 years, was admitted into St. Thomas's Hospital, under the care of Dr. Turney, on August 29th, 1904. Patient's father and mother were said to be suffering from syphilis at the time of his birth. There is nothing else of interest in either the patient's family or past history.

The present illness appears to date from the beginning of July of this year. The patient was having his holidays and noticed that he was unable to go about and enjoy himself as he wished to do, because he was so easily fatigued. His friends noticed that he was becoming anæmic. In the early part of August he was compelled to take to his bed owing to increasing weakness and severe persistent headache. On August 27th, he came to St. Thomas's Hospital for treatment, as he wished to leave England for South Africa as soon as it was possible.

On admission.—The patient was found to be intensely anæmic and in a very weak condition. The state of his mouth was extremely bad. There were a large number of stumps in both the upper and lower jaws, and a quantity of offensive pus oozed up around the fangs; the gums showed a great tendency to bleed, and were pale and spongy; large and tender glands could be felt in the submaxillary triangle and around the lower jaw.

Examination of the chest.—Respiratory system: There was some evidence of emphysema, otherwise the lungs were found to be normal.

Cardiac system.—The heart was found to be normal to inspection, palpation, and percussion, but a soft systolic murmur could be heard at the apex, and at the left base. The murmur was quite localised at both these situations. Radial pulse was 100, regular, and of fair tension. The vessel wall was thickened.

Abdomen.—Spleen descended about 1½ inches below the left costal margin, and this viscus also extended upwards for some distance above the normal limits. There was no friction rib heard. The spleen was of very firm consistence.

Liver.—There was a considerable increase of the area of liver dulness. The lower edge could be felt about the level of the umbilicus. The surface was smooth, and the free edge was hard.

There was nothing else abnormal in the abdomen; there was no evidence of ascites.

Lymphatic system.—There were no true glandular enlargements detected beyond what has already been referred to as a result of the septic condition of the patient's mouth.

Nervous system.—This did not present any abnormal features. The optic discs were found to be normal, and there was nothing abnormal detected on examination of the retinæ. The conjunctivæ were extremely pallid. There was no tenderness of any of the bones; there were no abnormal changes in the skin. Urine was acid, specific gravity, 1025, no albumen or sugar present.

Examination of the blood.—The red cells were counted by a modification of Gowers' method, the leucocytes by the Strong-Seligmann method. The hæmoglobin was estimated by Solly's modification of Olliver's hæmoglobinometer. The blood-films were stained by Leishman's method. I consider that it is impossible to over-estimate the value of this stain in hæmatology; in my experience it is far superior to any other, provided one obtains a good sample of the stain. It is equally good for stain-

TABLE I.

	August 31st, 1904. 1st examination.			Sept. 7th, 1904. 2nd examination.			Sept. 14th, 1904. 3rd examination.		
Erythrocytes per c.mm.	2,102,000			1,665,000			0,956,000		
Leucocytes per c.mm.	43,980			73,200			449,800		
Hæmoglobin per cent.	40·0			25·0			15·0		
Colour index	0·9			0·8			0·7		
Approximate ratio between leucocytes and erythrocytes	1—48			1—23			(nearly) 1—2		
Stained blood.	Per cent.	Per 1000 cells.	Per c.mm.	Per cent.	Per 500 cells.	Per c.mm.	Per cent.	Per 500 cells.	Per c.mm.
Polymorphonuclear neutrophils	2·1	21	924	1·6	8	1,171	0·4	2	1,799
Small lymphocytes	62·7	627	27,588	46·2	231	33,818	9·0	45	40,482
Large lymphocytes	34·0	340	14,960	48·8	244	35,721	83·6	418	376,032
Large hyaline cells	0·4	4	176	3	15	2,196	6·8	34	30,586
Mast cells	0	0	0	0	0	0	0	0	0
Eosinophils	0·8	8	352	0·4	2	292	0·2	1	899
Total mononuclear cells	97·1	971	42,724	98·0	490	71,735	99·4	497	447,100

ing the various blood-forming organs and various other tissues. The results of the examination of the blood, on three separate occasions is given in the foregoing table. It is impossible to over-estimate the importance of a complete examination of the blood in all blood diseases. A differential count of 500 leucocytes and the total number of each variety of leucocyte in a cubic millimetre of blood should always be obtained, otherwise the observations are of no scientific value.

Fresh blood and blood-films.—August 31st: Rouleaux formation (Hayem's method) was good. There was slight poikilocytosis present. A few microcytes but no macrocytes were seen. There were no nucleated red cells present and no degenerative changes in the red cells. Many of the leucocytes had ragged edges, and some showed a small central ring in the centre of the nucleus.

September 7th.—Rouleaux formation was present. There was slight poikilocytosis. Fibrin formation was very well shown. The appearances of the red cells were found to be almost identical with those obtained at the first examination.

September 14th.—There was no true rouleaux formation present. There was still only slight poikilocytosis. A few macrocytes and microcytes, but no nucleated red cells or degenerative changes in the red cells, were seen. Many of the mononuclear cells were very large, and a certain proportion of these cells contained some very small purple granules. The blood-films were carefully examined and something like 2000 cells were counted, but only three definite neutrophilic myelocytes were seen.

Agglutination of the erythrocytes.—If a patient's ear is punctured and the blood is normal, a definite red drop is noticed to appear at the seat of the puncture. If, however, the patient has only one million or less red blood corpuscles, as in the present case, the appearances are quite different. A drop of blood-stained serum is seen in which are suspended numerous minute red granules. If blood-film preparations are made, it is found that the red corpuscles are not separated as in healthy blood, because the cells are massed together in little clumps. Again, if the fresh blood is examined, it is found that there is absence of true rouleaux formation, but the red blood corpuscles are lying together in little clumps. Identical results are obtained

if a hanging drop preparation is made. The red blood corpuscles are, therefore, agglutinated in cases of very *severe* anæmia, and this phenomenon will be found to occur in the large majority of cases.

It has long been known that if physiological salt solution is added to normal blood the rouleaux formation is much less marked than normal. Mr. Shattock has shown that if horse serum is added to human blood, the rouleaux formation is much more marked than in normal blood. I have found that the *rouleaux* formation in cases of *polycythæmia* is always much more extensive than in normal blood.

Klein has shown that if we wish to make a suspension of plague bacilli for the purpose of serum diagnosis, we must use physiological salt solution, or else agglutination will be found to have occurred in the control culture. Douglas has recently found that a 0·1 per cent. salt solution is more suitable for the preparation of a suspension of plague bacilli than the stronger solution of salt. Crendirpoulo and Miss Amos have also shown that certain salts in certain dilutions inhibit the agglutination of micro-organisms. They found that a 1 per cent. solution of potassium chloride favours agglutination, wheras a 0·1 per cent. solution of the same salt prevents agglutination of the cholera vibrios. It is, therefore, evident from the above facts that various salts have an important bearing on the production of rouleaux formation, and agglutination of micro-organisms. Physiological salt solution can be shown to have a similar bearing on the agglutination of red blood corpuscles. If the blood, which has been obtained from cases of severe anæmia, and in which agglutination of the red blood corpuscles is known to occur, is mixed with a drop of salt solution, the red blood corpuscles will be found to lie quite isolated just as occurs when typhoid bacilli are mixed with salt solution. It is possible that the agglutination of the erythrocytes which occurs in cases of severe anæmia may be due to some alteration in the chemical constitution of the plasma, but at present there is not any direct proof either for or against such a view. It is also probable that this agglutination of the red cells which has been shown to occur in the blood as it escapes from a small puncture of the skin, and which is, therefore, probably present in the blood-stream, may be the cause of capillary thrombosis. This complication in severe

anæmia has been known to occur for some time past, but no satisfactory explanation has been offered. The idea that it is due to an agglutination of the red blood corpuscles in the capillaries is, as has been shown, a not unlikely explanation.

Bacteriology of the blood.—20 cubic centimetres of blood were withdrawn from the basilic vein of the right arm, and mixed with hot agar at the temperature of 44° C. The mixed blood and agar was poured into three large petri dishes and incubated at 37° C. On each plate small white colonies were obtained of the *Staphylococcus albus.*

Notes while the patient was in the hospital.—I will only mention the most important notes, those which have a direct bearing on the pathology of the disease.

Temperature.—There was pyrexia of an irregular remittent type during the whole period of the patient's illness while under observation in the hospital. There was never any very high temperature recorded. There were never any subcutaneous hæmorrhages or petechiæ seen. The condition of the mouth gradually became worse, and on several occasions the patient had a severe hæmorrhage from the gums. Two hæmorrhages were seen, for the first time four days before he died, in the right retina, and one or two dark spots which might have been due to capillary thrombosis. There was never any true glandular enlargement. The urine remained normal during the entire course of the illness. There was never any diarrhœa or vomiting. The bones were never tender.

Post-mortem examination (Dr. Gates).—The body was well nourished, and the subcutaneous fat was of a bright yellow colour. The mouth was in a septic condition, and enlarged glands were found in the submaxillary triangles. There was no enlargement of the tonsils or of the papillæ of the tongue.

Chest.—The *thymus gland* was atrophied. There were no enlarged mediastinal or bronchial glands. There were no pleural adhesions, but a small amount of slightly blood-stained fluid was present in each pleural sac. The lungs were very œdematous, but contained air throughout their entire substance. The right lung weighed 34 oz. and the left lung 24½ oz. The heart weighed 13½ oz. The valves were competent and healthy. The heart muscle was soft and very pale. Numerous punctiform hæmorrhages were seen beneath the endocardium of the right auricle.

The clot in the cardiac chambers and in the large blood-vessels was of a pale pink colour. The aorta was healthy.

Abdomen.—Spleen.—This viscus weighed 23½ oz. There was some evidence of old perisplenitis. The cut surface was pale and soft. There were no nodular enlargements visible to the naked eye. There was no enlargement of the mesenteric glands.

Hæmolymph glands. — Extending all along the vertebral column from the level of the cœliac axis downwards there were a very large number of large red, soft, and succulent glands.

Liver.—This organ was found to weigh 71½ oz. The surface was very irregular, and the capsule was thickened. There were no nodules visible to the naked eye. Dr. Box suggested that the liver should be examined for the free iron reaction. An intense blue reaction was obtained.

The *pancreas* and *adrenals* appeared to be normal.

Kidneys.—These organs were found to weigh 14½ oz. Both viscera were enlarged, and about the same size. *Right kidney:* The capsule was adherent; the surface was pale; the cortex was narrowed, and there were numerous small cysts on the surface beneath the capsule. *The left kidney:* The organ was of a purple colour, and the cortex was swollen. The capsule was adherent, but less so than in the case of the opposite kidney, and there were no cysts visible on the surface. No nodules were detected either on the surface or in the substance of either kidney.

The *intestines* from the duodenum to the rectum were normal. There was no increase of the lymphoid tissue. Numerous hæmorrhages were seen beneath the mucosa of the stomach. Enormous numbers of minute capillary hæmorrhages were visible on the surface of all the viscera, and in the adipose and connective tissue throughout the body; in fact, the skin appeared to be the only portion of the body which was exempt.

The brain appeared to be normal to the naked eye. An ossified plate, about half an inch by three quarters, was found in the falx cerebri.

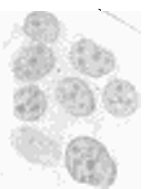
Bone marrow.—I took pieces of several ribs and also a portion of the right femur. The rib marrow was very soft, and not over abundant. It resembled thin pale, reddish-yellow pus. The femur was in a condition of chronic osteitis. The medullary cavity was obliterated and the outer surface of the bone was rough and irregular. A small quantity of bright yellow fat was

EXPLANATION OF PLATE I,

Illustrating Mr. L. S. Dudgeon's communication on "A Case of Acute Lymphocythæmia." (P. 114.)

FIG. 1.—Blood film, stained by Leishman's method. The red corpuscles have formed "clumps." The leucocytes are entirely of the mononuclear type. Some of the large cells are seen to have fine granules in the cytoplasm. Budding processes of the cytoplasm are clearly shown in one of the lymphocytes. Only one typical small lymphocyte is to be seen, viz. at the upper and right hand part of the field; a degenerated leucocyte with a very pale nucleus, but darker protoplasm, can also be seen. $\frac{1}{12}$ oil immersion.

FIG. 2.—A section of bone marrow stained by Leishman's method, from the case of acute lymphocythæmia described. The specimen shows that the bone marrow is extremely rich in cells, which are non-granular and mononuclear. The large proportion of these cells have a large pale nucleus, with granular markings. Only two of the cells have an indentation of the nucleus. $\frac{1}{12}$ oil immersion.



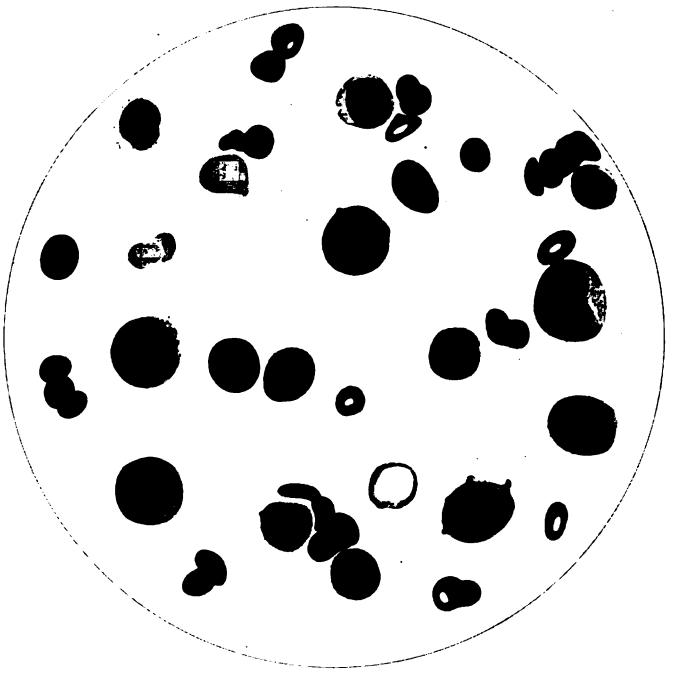
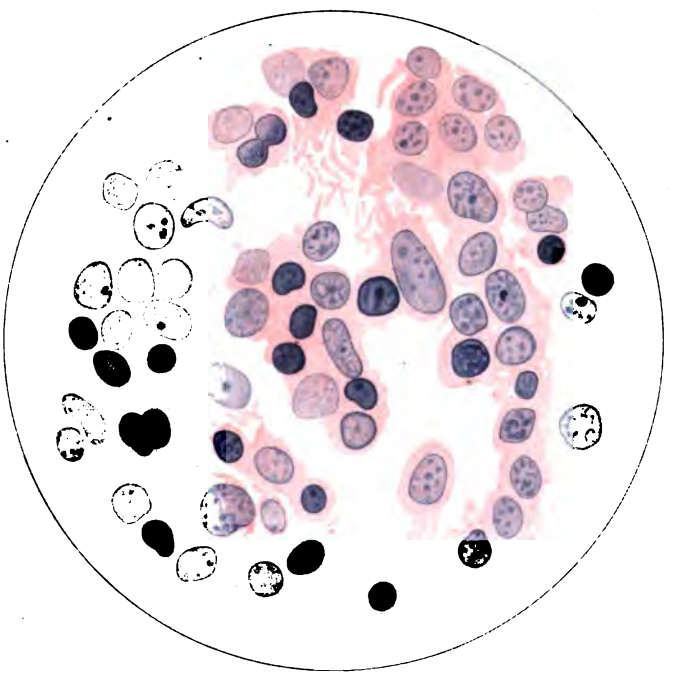


Fig. 1.

Fig. 2.



Lith. Anst. v. F. A. Funke, Leipzig.

obtained with difficulty from the centre of the femur owing to the spicules of bone which filled up the central canal of the bone.

Microscopical examination.—Small pieces of all the viscera were placed in various fixatives directly the autopsy was completed. Weak alcohol, 10 per cent. formalin, and Orth's fluid were used for this purpose. Sections were stained with hæmalum and eosin, Van Gieson's stain, Busch's fluid, ferrocyanide of potassium and weak hydrochloric acid, and Professor Leishman's eosin-methylene blue stain.

Microscopical histology.—Bone marrow (femur): The main bulk of the femur marrow was adipose tissue, but in places there were large masses of closely packed cells. No free iron reaction was obtained.

Sections stained by Prof. Leishman's method.—There were numerous small darkly-stained nucleated cells present, but the large proportion of the cells had a large pale nucleus which almost completely filled them. Only a very few showed an indentation of the nucleus. I failed to demonstrate any neutrophilic granules in any of these cells. No eosinophils or mast-cells were found in any of the sections. Only a few nucleated red blood corpuscles were seen.

Rib.—The cells were much more closely packed together than occurs in healthy marrow. No giant cells were seen, although a very large number of sections were examined; in fact, we did not observe any multinucleated cells. Only a slight reaction for free iron was obtained. The sections of the rib marrow which were stained by Leishman's method appeared to have an almost identical structure with the femur marrow. A few normoblasts, but no megaloblasts, were seen in the various sections. A differential count of the marrow cells was made. The total number of cells which were counted was 500. The result was as follows:

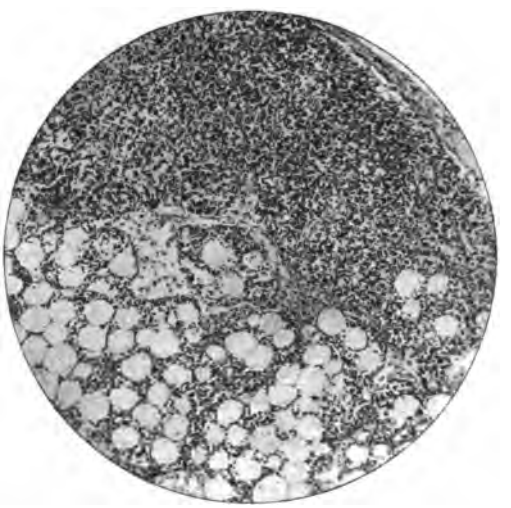
Small mononuclear cells	144	28·8
Large mononuclear cells	354	70·8
Large hyaline cells	2	0·4
	500	100·00

Eight normoblasts were seen while counting 500 white cells.

Hæmolymph glands.—The sections of the gland which were stained by Leishman's method were observed (with an oil immersion lens) to be very similar to the structure of the rib and femur

bone marrow and to the spleen. If the sections were examined with a low-power objective, it was found that the blood sinuses were packed with cells which with a high power were found to be similar to those already described in the bone marrow, although in a different proportion. These cells were also found in large numbers in the capsule, and also in the connective-tissue stroma of the gland. Only a slight reaction for free iron was obtained.

FIG. 24.



Lymphatic gland removed from the right groin and stained with hæmalum and eosin. Section shows large areas of fatty tissue which has replaced gland tissue. Examined with a ⅛ obj. and "B" eye-piece (Zeiss).

A differential count was made of the cells found in the hæmolymph glands, and the result was as follows:

Small mononuclear cells . .	269 .	53·8
Large mononuclear cells . .	228 .	45·6
Large hyaline cells . . .	3 .	0·6
	500 .	100·00

One normoblast was seen.

Lymphatic gland (groin).—The gland tissue was largely replaced by fat. These areas of fat were simply bounded by small mononuclear cells. Lymphocytes were present in large numbers in the capsule of the gland and in the connective-tissue septa. There was no endothelial cell proliferation to be seen throughout the

gland. The small lymphocyte was found to be the chief type of cell present, but there were also present cells which resembled the large mononuclear, which we have described as the predominant type in the bone-marrow.

Spleen.—Film preparations were made from scrapings of the surface of the spleen and were stained by Leishman's method. The large majority of cells present were similar to the large type of bone-marrow cell, in which we were unable to demonstrate neutro-

FIG. 25.

Section of liver stained with ferrocyanide of potassium and weak hydrochloric acid; counter-stained with eosin. Dark patches represent deposit of iron. Liver-cells are very much degenerated. Examined with a $\frac{1}{6}$ obj. and "B" eye-piece (Zeiss).

philic granules. No parasites were seen. There was no evidence of fat in the sections stained by Busch's method. There was only a small amount of free iron present. No Malpighian bodies could be identified in any of the sections. The capsule of the spleen was thickened, and coarse fibrous bands passed in all directions throughout the splenic tissue. The lumen of the blood-vessels in the capsule and in the fibrous bands were almost entirely filled with lymphocytes. No multinucleated cells of any kind were seen.

Liver.—There was a large amount of fat present in this organ. It was seen in the hepatic cells either as large drops, or most constantly as a very fine deposit. An enormous reaction was

obtained for free iron, and it is to be observed that the iron was scattered throughout the liver tissue, and was not confined to any definite region. The glycogenic reaction was negative. The capsule of the liver was thickened, and there was also a certain amount of fibrous overgrowth. The hepatic cells were very much degenerated, and in places were unrecognisable. The whole organ was riddled with round-celled infiltration.[1] The type of cell which was present in the various viscera appeared to be identical in its morphological and staining properties with the large mono-

FIG. 26.

Section of kidney, which shows large areas of round-celled infiltration which has extended in all directions throughout the renal tissue. Stained with hæmalum and eosin. Examined with a ⅓ obj. and "B" eye-piece (Zeiss).

nucleated cell already referred to in the bone marrow and elsewhere.

Kidneys.—There was a large amount of fat present in the tubules, and a few droplets could be seen in most of the glomeruli. The round-celled infiltration was very extensive in both kidneys. There was some thickening of the capsule present in the right kidney. The kidney tissue proper was largely replaced by fibrous tissue.

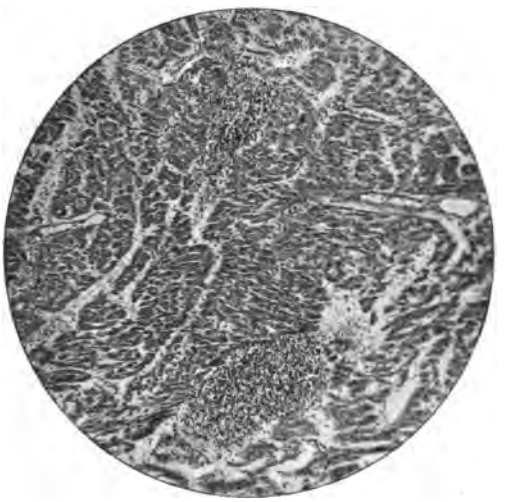
[1] Dr. Parkes Weber objects to the term "infiltrated," and prefers to use the word "permeated," as the latter term does not imply, which the former does in his opinion, that the cells have been deposited in the tissues from the blood-stream.

Both kidneys showed changes which were characteristic of chronic interstitial nephritis, but the right kidney more so than the left. The lymphocytic infiltration was most extensive in both kidneys; it affected all the structures, but perhaps more especially the renal tissue proper.

Lungs.—The alveolar walls were infiltrated with lymphocytes and the lumen of the capillaries was entirely filled with these cells, otherwise the lung tissue appeared to be normal.

Heart-muscle.—The capillaries beneath the epicardium and also

FIG. 27.



Heart-muscle, showing patches of round-celled infiltration. There are also scattered islets of cells between the various muscle-cells. Sections stained with hæmalum and eosin. Examined with a ⅓ obj. and "B" eye-piece (Zeiss).

those throughout the heart-muscle were packed with lymphocytes. There were also large patches of these cells throughout the muscular tissue. There was no increase of fibrous tissue. Many of the muscle-cells were degenerated. In some, the transverse striation was completely lost, and in others the nuclei were either degenerated or completely lost. The round-celled infiltration of the muscle was very clearly shown even between the individual cells.

No micro-organisms were seen in any of the microscopical sections of the various viscera.

Chemical analysis of the liver.—A specimen of the liver was sent to Dr LeSueur, Consulting Chemist to the hospital, who

issued the following report: The total weight of liver received amounted to 127·5 grammes. The inorganic residue measured 1·9 per cent., and the amount of iron was found to be 0·17 per cent. If we refer to Dr. William Hunter's work on pernicious anæmia, we find recorded an analysis of the liver in various diseases. The most important records are given below in a tabulated form:

	No. of cases.	Author.	Results (average).
Pernicious anæmia	4	Hopkins	0·458 per cent. of iron.
	6	Hunter	0·332 „ „
	2	Stockman	0·185 „ „
Total average for the twelve cases, 0·325 per cent. of iron.			
Leukæmia[1]	1	Hunter	0·140 per cent. of iron.
	1	Stockman	0·337 „ „
Average for the two cases, 0·238 per cent. of iron.			
Ankylostomiasis	5	Stockman	0·030 per cent. of iron.
	5	Rake	0·125 „ „
Average for ten cases, 0·077 per cent. of iron.			

Professor Stockman found, on an analysis of four healthy livers, 0·080 per cent. of iron. It is, therefore, obvious that there was considerable hæmolysis in my case. Professor Stockman found from an analysis of two cases of pernicious anæmia slightly more iron than Dr. LeSueur found in my case, while there was much more iron than in the recorded cases of ankylostomiasis. The two cases of leukæmia which are referred to in this paper showed much more evidence of hæmolysis than was found in my case. Dr. Hunter says, "The nearest approach to the average in pernicious anæmia is made in leukæmia and malaria, *i. e.* conditions which present clinically no difficulties in regard to diagnosis from pernicious anæmia."

Most observers will agree that the bone-marrow is a very important tissue in the pathology of acute lymphocythæmia, just as it is in myelæmia. The hæmolymph glands also appear to have a very important share in the pathology of this obscure disease. It is impossible to over-estimate the importance of a careful and complete examination of all the viscera, including the bone-marrow and glands, in this disease. My case shows the

[1] Dr. Hunter, unfortunately, does not state from w ich variety of leukæmia the results were obtained.

importance of this statement when we consider the difference which existed between a naked-eye and a microscopical examination of the femur marrow.

It would be preferable for the term "lymphatic leukæmia" to be replaced by either "acute leukæmia," *i. e.* using the term "leukæmia" in its very widest sense, or, still better, "acute lymphæmia" or "lymphocythæmia." To describe lymphocythæmia as "lymphatic leukæmia" is as incorrect as to describe myelæmia as "splenic leukæmia."

It has been suggested by various observers that acute lymphocythæmia is really acute myelæmia; that is to say, the cells which form such a characteristic feature of the blood are really myelocytes, not lymphocytes—a theory which was introduced by Askanazy.

Let us carefully compare the changes which are found in the blood in myelæmia and acute lymphocythæmia. The number of red and white cells in each disease is of little importance in the question now under discussion. If we examine the blood of a patient suffering from myelæmia, we find that there are certain changes in the red and white cells which are absolutely diagnostic of the disease. There is no known disease of adult life in which we find such enormous numbers of nucleated red blood corpuscles as in myelæmia. If a patient who is the subject of this disease suffers at any time from a hæmorrhage from the gums or elsewhere, we shall find that the number of normoblasts, megaloblasts, and microblasts is extremely large, especially the number of normoblasts. Polychromatophilic degeneration is usually well marked in such cases, but granular degeneration is not. Numerous macrocytes [1] and microcytes, and well-marked poikilocytosis is usually present. Now, if the case is an example of acute lymphocythæmia, we shall find an absolutely different picture. Nucleated red blood corpuscles in this disease are either extremely few or completely absent, even after severe hæmorrhages, as my case so well illustrates. Polychromatophilic and granular degeneration are either slight, or more frequently absent. It might be supposed that the number of nucleated red blood corpuscles was due to the fact that myelæmia is usually a chronic disease; such a view would, however, be erroneous.

[1] The most perfect macrocytes are found in the blood in cases of anæmia of the pernicious type.

Hermon Goldinier has recently reported a case of acute myelæmia in the 'Johns Hopkins Hospital Bulletin,' in which the patient only lived four months from the commencement of the illness. The author stated that normoblasts were common in the blood in his case, but that "an occasional megaloblast was present, perhaps one to every second or third field. No count of the nucleated red cells was made." This statement, however, requires modifying. If one megaloblast was present in every second or third field, a very large number of such cells would be seen in a differential count of 500 or 1000 leucocytes, when we consider that the patient had 260,000 leucocytes per c.mm. of blood. An extremely valuable case of acute myelæmia has been recorded by Billings and Capps. The patient's illness in this case began in August, 1899, but Dr. Richard Cabot, who examined the blood, found it to be normal. On September 20th, 1899, the patient was much worse, and had 2160 nucleated red cells in a cubic millimetre of blood, most of which were normoblasts. On October 7th, there were 2618 nucleated red cells in a cubic millimetre of blood. If we now consider the white cells in leukæmia, we are brought face to face with some very important facts. If numerous mast cells are found in a specimen of blood, it is justifiable to diagnose myelæmia. In normal blood we rarely find more than two mast cells while counting 500 leucocytes, but if 5 to 10 per cent. are found in the blood it is absolutely certain that the patient from whom the specimen of blood was obtained is suffering from myelæmia. In one case of myelæmia I found 17 per cent. of these cells in the blood.

In lymphæmia, however, this type of cell is only present in the blood in very small numbers and is *never* increased, but in many of the recorded cases of acute myelæmia there has not been any increase, or only very slight increase, of the number of mast cells.

In the literature, the term "myelocyte" is used in a very wide sense. There are numerous varieties of myelocytes, and to classify all forms under one head is not only incorrect, but most misleading. If the blood in myelæmia is carefully examined, at least four varieties of myelocytes (neutrophilic, eosiniphilic, basophilic, and amphophilic) will be found in every case. Those observers who consider that acute lymphocythæmia is really acute myelæmia—*i. e.* that the apparent lymphocytes are really myelocytes—appear to forget this fact. They use the term "myelocyte" as if every

myelocyte is neutrophilic. They even go further, and classify myelocytes as mononucleated cells; frequently non-granular. This is indeed a bold assumption, although it is not usually considered as such. It is well known that in chronic myelæmia there are a certain proportion of mononucleated cells which are usually very large cells and non-granular, and are often classified as myelocytes. These cells consist of a pale degenerated nucleus which is surrounded by a narrow rim of cytoplasm; but even here we are not absolutely justified in our conclusion. In acute leukæmia (lymphocythæmic type), however, the large majority of cells have a definite blue nucleus (eosin-methylene blue stain) surrounded by a rim of basophilic cytoplasm, and would be described as lymphocytes but for the unfortunate fact that they are present in enormous numbers. It is unjustifiable to my mind to describe these cells as non-granular myelocytes. If it was a purely clinical question, it would not matter whether they were called myelocytes or lymphocytes, but it is a matter of very great pathological importance, and, therefore, should be treated as such. In acute lymphæmia, definite neutrophilic myelocytes are found in very small numbers, and also large cells which resemble the large mononuclear cells such as are found in the blood in myelæmia, but the great majority of the cells are identical with the lymphocytes of normal blood, except that a good many of the large lymphocytes have ragged edges. Most of these cells also contain fine almost basophilic granules, but I must say, from a considerable experience of the fresh blood of man and animals, and also that stained by Leishman's method, that the majority of these cells are granular. It is well known that the basophilic granules which are found in the red cells in certain diseases are only to be seen in those cases in which some sample of this stain or polychrome methylene blue has been used. It also shows up the basophilic granules in the lymphocytes in normal blood and in the various anæmias, which otherwise would never have been demonstrated. Much more valuable results would be obtained in the future, if greater care is given to the diagnosis of a myelocyte. Many of the so-called polymorphonuclear neutrophils which are present in children's blood, and the large majority in the blood of kittens and puppies, are really polynuclear cells without any neutrophilic granules; but the nucleus of these cells is diagnostic. There is

nothing, however, diagnostic about the nucleus of a neutrophilic myelocyte, although in many of the neutrophilic myelocytes (large type), which are only found in chronic myelæmia, the nucleus is quite unlike anything which we see in normal blood or in any disease apart from leukæmia. The granules of a neutrophilic myelocyte, of course, are similar to the granules which are present in polynuclear neutrophils. If, however, those observers are correct who consider that the large lymphocytes which are found in the blood in acute lymphocythæmia are rarely non-granular myelocytes, then we have a condition of the blood which is unique, viz. almost the entire cells atypical myelocytes without neutrophilic granules. In the recorded cases of acute myelæmia, eosinophilic myelocytes have been present in every case, sometimes in large numbers. In Gordinier's case which has been already quoted, 4·1 per cent. of these cells were found in the blood. It is impossible to demonstrate basophilic granules with Ehrlich's stain, and, therefore, in those cases in which this was the only stain employed this type of cell would be overlooked.

In the recorded cases of acute myelæmia, polynuclear neutrophils and eosinophils have been considerably reduced in relative proportion but greatly increased in absolute numbers. In the other variety of acute leukæmia we have an entirely different picture. The lymphocytes amount to 80, 90, and even 99 per cent. of the total number of white cells, of which the large majority are usually large lymphocytes (myelocytes of some observers), but the polynuclear neutrophils, eosinophils, and mast cells are reduced relatively to a minimum, and often absolutely below the normal. Eosinophilic, basophilic, and amphophilic myelocytes are rarely met with. If we examine the bone-marrow in cases of acute myelæmia, we find that it consists almost entirely of neutrophilic myelocytes, and to a less extent of nucleated red blood corpuscles, eosinophils, eosinophilic myelocytes, and large mononuclear cells. In acute lymphocythæmia a few normoblasts are found, but the large majority of the cells are large and small mononuclear cells which do not contain any granules. A case has recently been reported before this Society of acute leukæmia, by Dr. Parkes Weber, in which the blood was not examined during life. A specimen of the blood was obtained at the autopsy and was examined by Dr.

Eastes, who found that the cells were chiefly non-granular lymphocytes, but 3·6 per cent. of eosinophilic myelocytes were also found. The bone-marrow, which was obtained from the shaft of the femur, was of a creamy blood-red colour, but not diffluent. It was examined by Prof. Muir, who found large numbers of eosinophils and mononuclear cells, and also in the spleen and bone-marrow, cells which had the characters of eosinophilic myelocytes. Prof. Muir remarks, "I have never seen eosinophile cells in such numbers in the tissues in lymphatic leukæmia, yet the case appears to be of that nature." It is most unfortunate that the blood was not examined during life in this case, as it appears from the result of the microscopical examination of the tissues that the case was atypical, and also that it is one, if not the only recorded case in which so many eosinophilic cells were present in the blood.

Leube has lately drawn attention to a disease to which he has given the name "leukanæmia." It is really a disease which has some of the characteristic features of pernicious anæmia and some of leukæmia. It has been suggested that some cases of lymphæmia and of myelæmia are of this class. In such instances the red cells show changes similar to those which are found in so-called pernicious anæmia, but there is a leucocytosis (lymphocytic or myelocytic) and leukæmic infiltration of the viscera. This case, however, does not bear any relation to the disease described by Leube as leukanæmia. In conclusion, I consider that acute lymphocythæmia is a disease with both definite hæmatological characters and certain changes in the various viscera, by which it can be separated from acute myelæmia.

My best thanks are due to Dr. Turney for giving me permission to make use of the entire pathological material derived from this case.

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10. *The occurrence of Bacillus enteritidis (Gaertner) in cows' milk.*

By E. Klein.

Amongst 39 samples of milk derived from different farms situated in the different English counties, the analysis revealed a condition of things which cannot but be regarded as disquieting. These samples were analysed at the request of Dr. Collingridge, the Medical Officer of the City of London, as to their possibly containing the tubercle bacillus. The milk on its arrival at the different railway stations in the City was taken directly from the churns in sterile bottles and brought to the laboratory. Of each sample 300 cubic centimetres were allowed to sediment, being kept for twenty to twenty-four hours in the ice-chest; the sediment was collected and injected into two guinea-pigs, one peritoneally, the other subcutaneously in the groin. After four weeks, the animals were killed and a careful *post-mortem* examination was made. Leaving out the occurrence of tubercle bacilli in about eight per cent. of the samples, I wish here particularly to draw the attention of those who are engaged in testing milk samples for tubercle bacilli to a condition of the infected guinea-pig which I have not seen described hitherto—namely, this: with ten samples—that is, 25·5 per cent.—the injected guinea-pigs, to all outer appearance in good condition, showed on *post-mortem* examination, either in the peritoneally or in the subcutaneously injected animal, or in both,[1] the spleen enlarged and containing sometimes few (four or five) sometimes many (over two dozen) whitish-grey nodules with purulent centre, the size of the nodules varying between that of a small pin's head and a hempseed, or larger. In the case of the subcutaneously infected animals there were no glands noticeable at the seat of injection in the groin; in the peritoneally injected animals occasionally few small purulent nodules were present in the omentum.

[1] In four samples in both animals, in four others only the subcutaneous, and in the remaining two only the peritoneal animal.

Film specimens of the material of the nodules showed no tubercle bacilli nor any other acid-fast bacilli and no *Bacilli pseudo tuberculosis*, but invariably and in great numbers oval to cylindrical bacilli, which, by cultivation in all media, were proved to belong to a single species, in all and every respect identical with the *Bacillus enteritidis* (*Gaertner*), readily distinguishable from the *Bacillus pseudo tuberculosis*. Sections through the hardened spleen showed the bacilli in smaller and larger masses and groups at the boundary between the central necrotic and the peripheral round-cell portion; in addition there were scattered through the central necrotic portions numerous isolated bacilli.

The culture tests were made in parallel series both with our typical laboratory *Bacillus enteritidis* (*Gaertner*) and with subcultures from the primary agar plate cultures of the spleen nodules of every one of the above guinea-pigs: in gelatine surface and in gelatine shake; in agar surface, in broth, and on potato, in neutral red broth, in ordinary milk, and in litmus milk, in MacConkey fluid, in lactose litmus peptone, and on Drigalski medium; the bacilli were examined in the hanging drop, in stained specimens, in gram; their flagella were stained, and their emulsion was tested with the blood-serum of rabbit previously immunised by intravascular injection with our laboratory *B. Gaertner*. The cultures were tested for virulence by subcutaneous injection of guinea-pigs, and it was found that $\frac{1}{50}$ to $\frac{1}{100}$ part of a cubic centimetre of a twenty-four hours' broth culture, as also a mere trace of a colony of a recent agar culture, caused acute septicæmic infection and death, the spleen being found enlarged, dark, soft, the blood of the general circulation and the tissue of the spleen being crowded with the bacilli.

The production of alkali in litmus milk, the production of blue colonies on Drigalski medium, flagella numerous, long, thin and wavy, and the rapid and decisive agglutination with blood-serum of rabbit prepared with the laboratory *B. Gaertner* are the conclusive tests by which identity of our milk bacillus with the typical *B. Gaertner* was established.

Since in the guinea-pigs injected with the milk the process appears to be of a chronic character, it was surmised that this result was owing to the number of bacilli in the milk being limited, as is indeed suggested by the fact that out of the ten incriminated samples with each of six a positive result was produced

only in one of the two animals injected. Direct experiment confirmed the correctness of this surmise, for it was shown that with smaller doses of culture of the bacillus, *e. g.* $\frac{1}{1000}$, $\frac{1}{2000}$, and $\frac{1}{4000}$ of a cubic centimetre of a twenty-four hours' old broth culture, the injected guinea-pigs remained alive, and after nine days commenced to develop the above condition, viz. the formation of miliary nodules in the enlarged spleen, which nodules gradually softened and became purulent in the centre. From this it seems justifiable to conclude that the production of the chronic purulent foci in the enlarged spleen of our milk guinea-pigs was due to the relative scarcity of the bacilli in the milk.

It is disquieting to reflect that such a large percentage of the milk samples contained the *B. enteritidis* (*Gaertner*), because if such milk were kept for some time in a warm place, or if such occurrence happened during the warm months of the year, the consumption of the raw milk might be fraught with undesired consequences, the milk being, it will be remembered, a good medium for the multiplication of the *B. Gaertner*, and remaining unaltered to the unaided eye.

As a matter of fact, after feeding guinea-pigs and mice with milk culture, or with milk to which culture had been added, half of their number were found dead on the fifth day, the lower ileum to the extent of several inches just at and above the ileo-cæcal valve being found distended by and filled with sanguineous mucus, the mucous membrane in a state of extensive hæmorrhage.

Inquiry of the usual kind made at the different farms from which the infected samples were derived failed to discover any noticeable disease amongst the cows, but the general conditions of the sheds and their surroundings: the milking, and the collection of the milk were of the usual kind—namely, dirty.

Addendum.

The chief differential characters between the bacilli of the Gaertner group and the *Bacillus pseudo-tuberculosis* (A. Pfeiffer) with which a confusion might be made are these: the bacilli of the Gaertner group are highly mobile, multiflagellated, the *B. pseudo-tuberculosis* is non-mobile; the bacilli of the former produce gas in gelatine shake culture, the pseudo-tuberculosis does not do so; the bacilli of the former produce uniform turbidity in broth and in phenol broth, the latter form granules and flocculi in broth cultures, the broth remaining clear;

the bacilli of the former produce acid and gas in MacConkey fluid, the latter do not; the effect of even large doses of the *Bacillus pseudo tuberculosis* injected subcutaneously in the groin of guinea-pigs produces a gradually increasing tumour of the inguinal glands, followed in one to two weeks by suppuration, with the development of necrotic nodules in the spleen, liver, and lungs; small doses of the bacilli of the Gaertner group cause acute septicæmic infection.

January 17th, 1905.

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11. *A note on the use of acid media in the isolation of* B. pestis.

By W. C. C. Pakes and F. H. Joseph.

During the course of the year 1903 several suspicious cases of plague were examined in the Government laboratories, and the ubiquity of the pneumococcus in the Transvaal led us to search for an easy method of isolating the *B. pestis* from such concomitant organisms as the pneumococcus. The idea really originated from the examination of the organs of a native who had died of a definite adenitis which was proved to have been due to the pneumococcus.

At the time of the recent outbreak of plague on the Witwatersrand we found that when the sputum or lung juice of patients suffering from the pneumonic form was inoculated into rabbits and guinea-pigs (in the absence of tame rats) the inoculated animal sometimes died apparently of plague and sometimes of pneumococcic septicæmia.

Although in the ordinary way guinea-pigs are not nearly so susceptible to the pneumococcus as are rabbits, nevertheless we found that occasionally the guinea-pig succumbed, and the only recoverable organism was the pneumococcus, even though morphological plague organisms had been seen in the smear preparations of the original sputum or lung.

The work of many investigators has shown that the pneumococcus is intolerant of certain media, and experiments were commenced with a variety of them. As the most hopeful results appeared to follow from the use of acid broth, accurate observations were made, among others, upon the comparative growth of the two organisms on media of different degrees of acidity.

Ordinary nutrient broth was standardised according to Eyre's

method, and the two organisms were grown side by side. The results we obtained are tabulated below:

Reaction of media to phenolphthalein.	*B. pestis.*	Pneumococcus.
− 5	No growth	—
− 2	„	—
Neutral	„	—
+ 10	Fair growth	Good growth
+ 15	„	Very fair growth
+ 20	Very fair growth	Slight growth
+ 25	„	No growth
+ 30	Fair growth	„
+ 35	Not so vigorous	„
+ 40	Slight growth	„
+ 42	„	„
+ 45	Traces of growth	„

From the above it will be seen that the pneumococcus will grow slightly in broth of an acidity of +20, and will not grow in +25. With the *B. pestis*, however, a good growth is obtained in broth having a reaction of +40, while the organism will multiply in broth of an acidity as high as +45.

When, therefore, as not infrequently happens in this country (the Transvaal), a sputum is examined that contains organisms which, from the microscopic appearances, consist of a mixture of the *B. pestis* and the pneumococcus, and it is desirable to make absolutely certain of the diagnosis, it has been found very useful to inoculate +25 or +30 acid broth with the material direct, and incubate at 37° C., and when necessary to inject guinea-pigs or rabbits with the resulting cultivation. By this means the pneumococcus has, on several occasions, been entirely eliminated and the animals in question have died of plague infection.

It is true that other bacteria will grow in broth of this acidity, and that consequently the test is not an absolutely infallible one; but such organisms are not frequently met with in a suspicious plague sputum, and therefore in many instances a final positive result has been arrived at, when direct inoculation has left the matter still in doubt.

In actual practice during the whole time of the outbreak, except at the very first, any specimen of lung or sputum which contained pneumococci as well as bacilli indistinguishable from

the *B. pestis* was inoculated into the subcutaneous tissue of the groin of a guinea-pig, and at the same time acid broth was inseminated, so that there would be a double chance of obtaining the bacillus in pure culture, and, therefore, of arriving at an unambiguous diagnosis. *January 17th*, 1905.

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12. *Fugent—a new stain.*

By F. H. JOSEPH,
Assistant Bacteriologist, Government Laboratories, Johannesburg.

WHILST endeavouring to obtain a stain for the demonstration of the capsules of the pneumococcus and other similar bacteria, a solution was obtained which gave promise of good results. This stain consisted of a mixture of alcoholic solutions of methylene blue, fuchsin, and gentian violet. After a considerable amount of work, the following formula has been obtained:

(1) Methylene blue satd. alcoholic sol. 4 parts.
(2) Basic fuchsin „ „ „ 3 parts.
(3) Gentian violet „ „ „ 5 parts.

The above are all Grübler's aniline dyes.

This mixture is made and allowed to stand for from three weeks to a month, when it has matured and is ready for use. It has been found that it requires this interval to mature, but that having matured, it does not deteriorate with time.

In order to prepare it for actual use, one part of the stock stain is diluted with two parts of distilled water. The diluted stain cannot be kept indefinitely; it has been found in practice that it ceases to stain satisfactorily after about three weeks.

In order to demonstrate the capsules of bacteria, a coverslip preparation is made of blood effusion or tissue juice, and allowed to dry thoroughly in the air. It is then placed in the stain without fixing in any way, and allowed to remain for forty-five seconds, washed in water, dried, and mounted. The bacteria when seen under the microscope are of deep red colour, whilst the capsules are of a light violet tint and appear with a well-defined edge.

As the stain showed a marked differential power, it was tried with various organisms and particularly with the *B. pestis*.

During the recent outbreak of plague on the Witwatersrand opportunity has been taken of the large amount of available

material to make exhaustive trials of the value of the stain, and the results are very satisfactory, since it is both a quick and clean stain. The technique necessary to bring out the best results is as follows:

The film, having been made and allowed to dry, is passed eight or ten times through the top of the Bunsen flame, at the rate of between two and three times a second. Care must, of course, be taken not to scorch the film by passing it through too slowly. It is allowed to remain in the stain for about 45 seconds, washed, dried, and mounted.

When examined under the microscope, the bacilli are seen to have deep violet or blue polar granules, whilst the body of the bacillus is stained of a light red colour. In blood specimens the red discs are coloured red, and the nuclei of the leucocytes a deep violet or blue, but not so deep as the polar granules of the bacilli. It is not claimed that this stain can be used to determine the presence of the *B. pestis* by microscopic appearance alone, but the polarity is much more easily seen than if the preparations are stained with methylene blue, fuchsin or gentian violet alone, largely on account of the double staining, and therefore marked contrast, exhibited.

It is hoped that, with some slight modification in the technique, the stain will be found useful in demonstrating the presence of the capsules of pneumococcus, etc., in the sputum direct, and trials are being made to that end.

January 17th, 1905.

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13. *An intra-intestinal cystic swelling in connection with the ampulla of Vater.*

By R. S. Trevor.

The specimen of an intra-intestinal cystic swelling in connection with the ampulla of Vater, which it is my privilege to show you this evening, was found during the necropsy on the body of a young man who succumbed to the effects of a perforated duodenal ulcer.

The man was aged 24 years, and his occupation was that of a groom. For some years he had suffered from dyspeptic symptoms, which had latterly become aggravated. For fourteen days prior to his admission to St. George's Hospital he had had pain and vomiting after meals but no hæmatemesis. On the morning

of the day before he was sent to the hospital the pain became very severe and vomiting was frequent. On admission the man presented all the typical features of intra-peritoneal perforation of some hollow viscus and was in a very critical condition. Operative measures were decided upon at once and when the abdomen was opened a perforated duodenal ulcer was found and sutured. There was general peritonitis with free gas and turbid fluid in the peritoneal cavity, which was consequently irrigated. The operation, which was performed about 28¼ hours after perforation had occurred, was unfortunately of little service, as the man died on the following day.

The necropsy revealed no lesions of importance within the thorax or in the abdominal viscera, with the exception of the upper part of the alimentary canal. There was general peritonitis, with a thick layer of fibrin on the under-surface of the diaphragm, the left half of the anterior abdominal wall, and in the pelvis.

The stomach, duodenum, pancreas, and liver were removed *en masse* and are shown in the specimen.

The stomach was somewhat dilated. Two ulcers can be seen in the mucous membrane, the larger and more chronic upon the posterior wall near the lesser curvature and close to the pylorus, the smaller and more acute on the anterior wall immediately opposite the former. Neither of these ulcers have perforated.

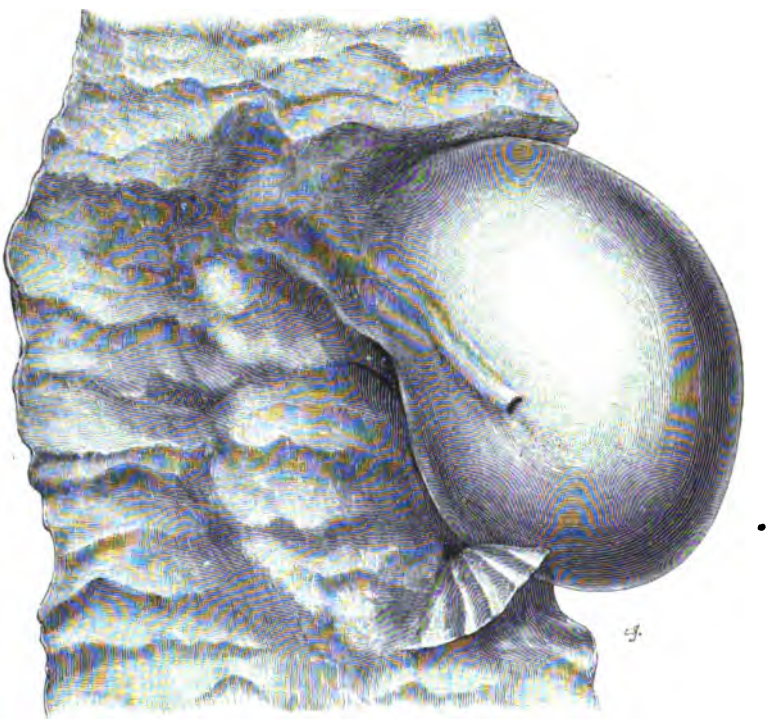
Just outside the pylorus in the commencement of the duodenum on its anterior wall is a large peptic ulcer, which has perforated and which has been surgically sutured.

The most striking lesion in the duodenum, however, is an oval cystic swelling of about the size of a tangerine orange, springing from the antero-internal aspect of the wall of the descending portion and projecting into the lumen. Running down upon the right-hand side of the swelling from its upper part a ridge can be seen, and this ridge terminates in a crescentic opening on the cyst wall, the concavity of the crescent being directed downwards (Fig. 28).

Pressure upon the gall-bladder causes an escape of bile through this opening and through this opening only. At the same time the ridge already described is thrown into greater prominence. These facts, in conjunction with the entire absence of any other biliary papilla in the duodenum, suggest that the ridge is formed by the common bile-duct and that the crescentic opening is the

duodenal orifice of the ampulla of Vater. This view is readily confirmed by the passage of a probe into the opening, when without any difficulty it can be pushed upwards and felt in the hepatic duct, and further by the escape through the same opening of a second probe passed into the duct of Wirsung exposed by transverse section of the body of the gland. A piece of copper wire and a bristle are now shown in the common bile-duct and the duct of Wirsung respectively.

FIG. 28.



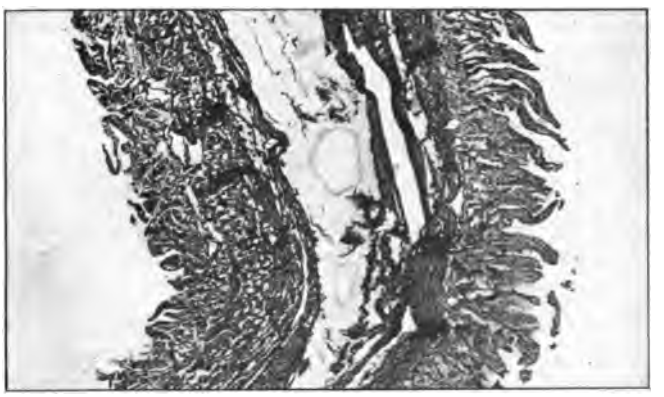
The cyst is shown pushed over towards the middle line so as to expose the course of the common bile-duct and its opening on the cyst wall. (This opening has been drawn rather too small.)

Compression of the cyst itself also causes a flow of bile from the crescentic opening. Hence there must be some communication between the cyst and the common bile-duct or the ampulla of Vater. Inspection through the " window " cut into the lower surface of the cyst reveals the bile-stained condition of its inner wall, for it was found to contain when opened about 3 ounces of green bile free from all traces of sand or calculi.

At the upper end of the cyst cavity a small aperture can be seen which allows the copper wire and bristle to be identified lying side by side, thus showing that the cyst communicates with a cavity common to the two ducts, or in other words, with the ampulla of Vater. The communicating aperture can be shown, though the incision made into the common bile-duct, to lie nearer to the duodenal opening of the ampulla than to the orifice of the pancreatic duct.

The cyst springs from the duodenum form an oval base measuring in its long axis, which lies in the length of the gut, $1\frac{5}{8}$ inches, and in width $\frac{11}{16}$ inch. The outer surface of the cyst

FIG. 29.



Photomicrograph of the wall of the cyst. The right-hand side shows the duodenal mucosa, the left shows the mucosa lining the cyst.

and the wall of the duodenum on either side of it show no trace of valvulæ conniventes. The first of the folds, however, which crosses the gut at the lowest edge of the cyst-base is prolonged on to the cyst-wall as a **V**-shaped process.

Microscopical examination of the wall of the cyst shows that it is lined both inside and out with intestinal mucous membrane-bearing villi. The bile-sodden condition of the tissue renders it difficult to stain properly, but in spite of this both villi and crypts of Lieberkühn can be made out. The villi are entirely denuded of epithelium. Between the two layers of mucous membrane only submucous tissue is present (Fig. 29).

The microscopical structure of the lining membrane of the cyst disposes at once of three possible hypotheses as to its

nature. It is not the result of ulceration of the ampulla, as, for instance, from the presence of a gall-stone, and the subsequent formation of an abscess beneath the duodenal mucosa. It cannot be an invaginated duodenal pouch, neither can it be a retention cyst of an accessory pancreas in the tissue of the bile papilla, the occasional occurrence of which, in this situation, has been described by Opie (1).

There remain, in my opinion, two possible explanations. The first is that the cyst is a hernial protrusion of the lining membrane of the ampulla through a weak spot in the wall of the latter, with subsequent slow distension of the sac with bile. I have, however, reluctantly abandoned this (to me) very tempting view because of the want of certain evidence that the ampulla of Vater is normally lined with mucous membrane identical with that of the intestine, especially as regards the presence of villi. Pilliet (2) describes the mucous membrane of the ampulla as normally containing glands, which from his description appear to me to be mucous glands, but he makes no mention of villi. Oser (3) merely states that the diverticulum Vateri is lined with mucous membrane. Letulle and Natan-Larrier (4), in their paper on the "Région Vaterienne du Duodenum et Ampoule de Vater," describe the histological structure of the ampulla from sections of specimens in which the two ducts open separately on the papilla, and there is consequently no ampulla at all! I have recently examined, for this special purpose, three specimens in which an undoubted ampulla was present, but I have not seen anything in the lining membrane resembling an intestinal villus. Unfortunately, in not one of my specimens is the epithelium preserved, but mucous glands are present in small numbers. The general impression left upon my mind by the study of these sections is that the structure of the ampulla more closely resembles that of the bile-duct than that of the intestinal mucous membrane.

The alternative suggestion which I put forward is that the cyst is due to abnormal fusion in the middle line of two folds of mucous membrane, which are often normally present on either side of the biliary papilla. According to Letulle and Natan-Larrier (5) the most frequent type of termination of the bile and pancreatic ducts in their series of specimens was characterised by a fairly prominent papilla situated above a fossa or groove, bounded on either side by a vertical fold of mucous

membrane. These folds are united over the upper surface of the papilla and are continued downwards on either side of it to form the boundaries of the fossa already mentioned, at the lower end of which they are again united and prolonged downwards in the form of a solitary band or frænum. The fossa may be either oval or circular, and is regarded by Letulle and Natan-Larrier as a malformation. The folds of mucous membrane which bound it are always united above on the upper surface of the papilla, upon which the two ducts open separately. The general appearances are shown in Fig. 30.

Oser (6) described a similar condition, with this difference, that

FIG. 30.

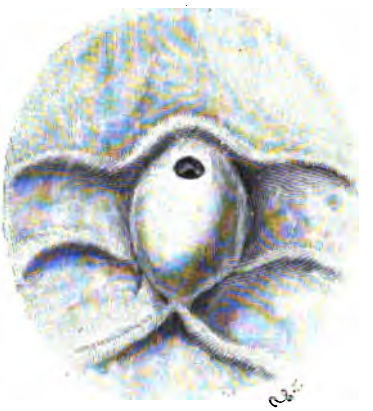
(After Letulle and Natan-Larrier.) Biliary papilla situated at the upper extremity of a fossa, which is bounded on either side by a fold of mucous membrane. The folds are united above, and form a covering to the upper surface of the papilla, whilst below they are joined and prolonged into a single fold or frænum.

the duct of Wirsung opens into the bile-duct, which then opens directly into the gut at the upper end of a groove formed by two folds of mucous membrane. These two folds are united above, but there is no projecting papilla between them. The groove is regarded by Oser as a cleft of the diverticulum Vateri.

There is little doubt that congenital peculiarities of the Vaterian region are not uncommon. It seems to me clear that, if as a congenital anomaly, the two folds of mucous membrane referred to above were fused together in the middle line so as to enclose the fossa between them, a cyst lined inside and out with true intestinal mucous membrane would be the result. Such a possibility I have represented in Fig. 31.

Further, if the upper line of union passed *across* the opening of the biliary papilla, a not unlikely possibility since the folds are

FIG. 31.



Cystic swelling which would result from fusion in the middle line of the folds bounding the fossa shown in the preceding figure.

FIG. 32. FIG. 33

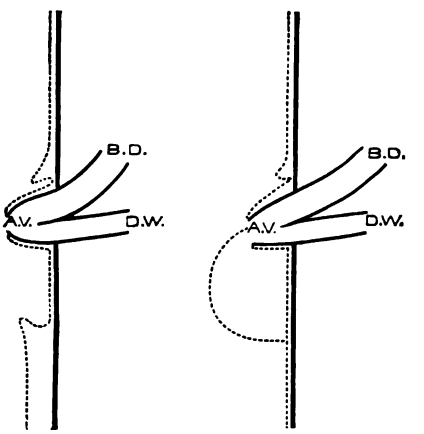


Fig. 32.—Section diagram of Fig. 30.
Fig. 33.—Section diagram of Fig. 31.
The diagrams represent longitudinal sections of the duodenum passing through the biliary papilla. B.D., Bile-duct. D.W., Duct of Wirsung. A.V., Ampulla of Vater. Dotted line, duodenal mucous membrane bearing villi. (In Fig. 33 the dotted line, where not in contact with the black continuous line, represents a double layer of mucous membrane covered on both sides with villi.)

described as normally fused to the upper surface of the papilla, the communications of the ampulla with the intestinal canal and

with the cyst are readily explained. These remarks will be made clearer by reference to the section-diagrams Figs. 32 and 33.

The crescentic orifice of the cyst is likewise explained, as the two folds are normally arched over the biliary opening. The relative positions, as seen in the specimen, of the outer opening on the cyst wall and the internal opening into the ampulla of Vater are the outcome of the gradual distension of the cyst with bile, aided by the traction produced upon the upper parts of the cyst by the weight of its contents.

The interest of the specimen, apart from its rarity—for I have been unable to find a record of another specimen quite resembling it—lies in the absolute lack of ill effects attributable to its presence. The dyspeptic symptoms and the gastric and duodenal ulceration are all compatible with the existence at some time or another of lesions of a catarrhal nature in the upper part of the intestinal tract. Yet there is a striking want of any evidence pointing to inflammatory changes in the bile or pancreatic ducts or in the pancreas, such as might have been expected from the spread of infection from the duodenum to a stagnant or nearly stagnant collection of bile so closely in connection with it.

In conclusion I wish to express my thanks to Dr. Rolleston for his kind help, to Mr. Laurence Jones for his drawing of the specimen and to Dr. Harold Spitta for the photo-micrograph.

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1. *Opie.*—'Diseases of the Pancreas,' p. 60.
2. *Pilliet.*—'Comptes Rendus Soc. Biol.,' 1894, p. 549.
3. *Oser.*—"Diseases of the Pancreas," 'Nothnagel's Encycl.,' English Trans., , p. 19.
4. *Letulle and Natan-Larrier.*—'Bull. d. l'Soc. Anat.,' t. xii, 1898, p. 501.
5. *Letulle and Natan-Larrier.*—*Loc. cit.*, p. 498.
6. *Oser.*—*Loc. cit.*, p. 25.

December 6th, 1904.

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14. *Toxæmic jaundice and interstitial hepatitis.*

By JOHN F. H. BROADBENT.

THE paper which I venture to bring before you this evening deals with five cases of hepatic disease of obscure etiology. The first of these clinically and pathologically presented many of the

characteristics of the disease known as acute yellow atrophy of the liver, and falls under the category of toxæmic jaundice, in that the jaundice was independent of any obvious mechanical obstruction in the bile-ducts, and appeared to be due to the absorption of some virulent toxin from the intestines.

In the remaining three cases the pathological change in the liver was a diffuse interstitial fibrosis possibly due to some prolonged chronic toxæmia or to cicatrisation after an acute destructive lesion. Clinically they were noteworthy for the abrupt onset and severe nature of the final symptoms, the absence of a history of any of the common causes of cirrhosis, and the diversity of age of the patients, the youngest being 10 years and the oldest 73 years of age. Macroscopic and microscopical specimens of the liver in each case are on the table, and I will first give a brief clinical account of the cases and the pathological appearances in the liver and then proceed to discuss the etiology of the condition.

The first case is that of a young girl, aged 17 years, who was employed as a domestic servant. She was admitted to St. Mary's Hospital under Dr. Lees on January 7th, 1902. She had been anæmic for some five months, but first became definitely ill one month before admission, when she had severe pain in the right hypochondriac region. She became jaundiced five days later. The pain persisted and the jaundice increased and ten days before admission her temperature rose to 105°. There was no hæmatemesis or melæna and no vomiting. The temperature remained high, and on admission was 104° F. She was deeply jaundiced, the liver was tender and its lower margin could just be felt under the ribs. Urine: dark orange; s. g., 1010; trace of albumen; no leucin crystals, but trace of tyrosin; urea, 1·6 per cent. Heart and lungs normal. The jaundice and pyrexia persisted. She became delirious and passed into a "typhoid" state, dying on January 12th, a week after admission and five weeks after the onset of the jaundice. No history suggestive of syphilis in her own or her family history could be obtained. She had been in service for four years and there was no history of alcoholism. The only illness known was an attack of influenza followed by pneumonia nine years previously, but from this she had made a good recovery. At the autopsy the liver was found to be small and shrunken, weighing only 40 ounces. There was

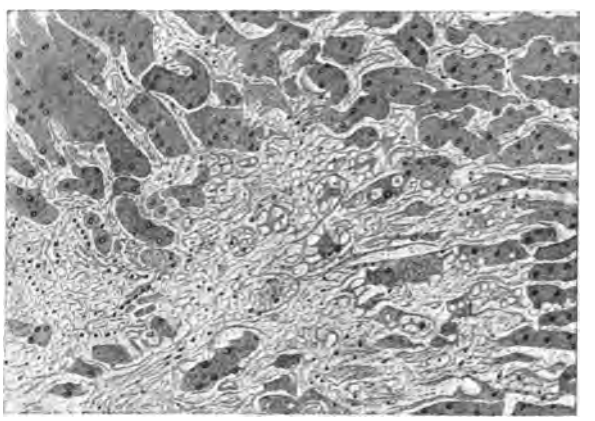
no perihepatitis, and the gall-bladder and biliary passages were normal and did not contain any gall-stones.

On section the liver showed red hæmorrhagic areas alternating with pale yellow fatty areas, and was deeply stained with bile throughout.

The spleen was enlarged, 9 ounces in weight, soft and diffluent, dark in colour, and intensely congested.

The kidneys were large, weighing 7 ounces; the cortex was pale and swollen, with numerous hæmorrhagic ecchymoses.

FIG. 34.



Section of the liver from Case 1, showing acute destruction of liver-cells towards the centre of a lobule, with no attempt at cell proliferation.

Heart 17 ounces, numerous petechial hæmorrhages beneath the epicardium. Muscle soft and pale.

Microscopically.—The liver shows areas of liver-cells, some not much damaged, others in various stages of disintegration and fatty degeneration, with numerous hæmorrhages, alternating with areas which consist of a network of areolar tissue which appears to be the supporting structure of what were once liver-cells. The destruction is greatest round the intra-lobular veins. Deposits of bile pigment are seen in many of the cells, and sections treated with ammonium sulphide show free iron in the cells.

The heart-muscle, stained with osmic acid, shows advanced fatty degeneration. The kidneys show an advanced degree of cloudy swelling, with fatty degeneration.

On seeking for the explanation and cause of the jaundice in

this case, no obstruction could be found in the larger bile-ducts, and there was no new formation of fibrous tissue in the portal canal which might have constricted the smaller biliary canals, so that the jaundice appears to be independent of obstruction, a condition for which various explanations, such as suppression of liver function, paralysis or spasm of the bile-ducts from nervous influences, etc., have been offered. The pyrexia and severe constitutional symptoms, with the extreme destruction of liver-cells, suggest some acute toxic infection of the liver, and the case seems to fall under the category described by Dr. William Hunter * as toxæmic jaundice. The explanation he gives of the jaundice in this class of cases, is, that the toxic and injurious products conveyed to the liver by the portal vein are excreted in the bile, and set up a desquamative catarrh in the smaller bile-ducts, which causes obstruction to the flow of bile through their lumen.

The various known causes of toxæmic jaundice as classified by Dr. William Hunter are as follows :

(1) Poisons, such as phosphorus, toluylendiamin, arsenuretted hydrogen, and snake venom.

(2) Certain fevers—yellow fever, malaria, typhus, scarlet fever, and pneumonia.

(3) Some obscure diseases of unknown etiology—Weil's disease, acute yellow atrophy, epidemic and malignant jaundice.

In these diseases severe constitutional symptoms are usually present in addition to the jaundice, namely pyrexia, hæmatemesis and melæna, and delirium frequently terminating in coma.

In the case under discussion the causes enumerated in the first two groups are excluded by the clinical history, and it appears most to resemble the condition classified as acute yellow atrophy. Of the etiology of this disease little is known. In the present case there was no history of pregnancy, with which its onset is sometimes associated, and bacteriological investigations gave negative results. The clinical history and pathological appearances *post mortem* suggest as the cause some virulent toxin, the stress of which fell primarily on the liver, presumably conveyed to the liver by the portal vein and generated in the intestinal canal.

The remaining cases come under a different category and may be

[1] Clifford Allbutt's 'Medicine,' vol. iv, p. 92.

classified as interstitial hepatitis or fibrosis, possibly due to a chronic toxæmia, though in the abrupt onset and nature of the final symptoms they present some analogy to the case just discussed.

The first of these cases (Case 2) is that of a girl, aged 22 years, who was admitted under Dr. Lees, September 29th, 1903, for swelling of the abdomen and jaundice.

History.—She had not felt well since the previous Christmas. Had influenza in February, but did not seem to get over it. She took fresh "chill" in April, when she first began to be jaundiced. The jaundice did not pass off, and became much worse in June, when the abdomen became somewhat distended. Two weeks before admission the distension of the abdomen increased very much and the feet and legs became swollen. She had never had any pain in the abdomen. No history of alcohol or syphilis.

On *admission*, jaundiced; temperature, 100·8°; abdomen greatly distended from ascites. Legs œdematous. Liver not felt. Heart normal. Lungs: signs of fluid at right base. Urine: s. g., 1030, no albumen; bile pigment present, but no leucin or tyrosin.

She improved for the first few days, and the temperature fell to normal, but on October 3rd it rose to 100·4°, and on October 2nd to October 3rd to 101·8°. She became very short of breath, and the abdomen tender and tense. A large quantity of clear yellow fluid was evacuated from the abdomen. The temperature fell to 96° on October 5th, and on October 6th she became noisy and delirious, and died the next day, nine days after admission.

At the autopsy there was fluid in the peritoneum, but no lymph or signs of recent peritonitis. Liver: the capsule was thickened, hard, and leathery from old perihepatitis, and there was some puckering and scarring of the surface in places. Otherwise it was smooth. On section the liver appeared to consist of two distinct portions, one dull brick-red in colour and homogeneous, the other composed of irregular polygonal areas of yellow bile-stained liver-cells embedded in a ground substance of fibrous tissue. The gall-bladder was not enlarged. It did not contain gall-stones, and the ducts were pervious. The lungs were congested with areas of hæmorrhagic ecchymoses. Heart normal.

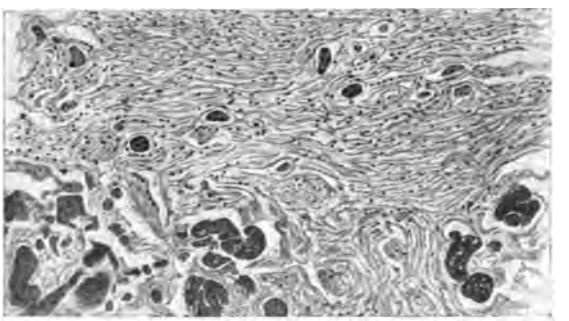
Kidneys congested. On section showed thickening of vessels

and some fibrosis round the glomeruli with atrophy and cloudy swelling of the epithelium of the convoluted tubules.

Pancreas normal.

The liver.—Microscopically the red area is seen to consist almost entirely of fibrous tissue, with numerous bile-ducts, in which scarcely any trace of liver-cells is seen. The fibrous tissue is not arranged in regular bands, but forms a dense coarse network. The bile-ducts are thickened, and the epithelium is desquamating. In the portion of liver where islands of liver-cells are present they are scarcely recognisable as such. The nuclei have completely disappeared, and the cells are represented by swollen amorphous granular masses.

FIG. 35.



Section of the liver from Case 2, showing dense fibrous tissue with absence of liver-cells.

This case bears a striking resemblance to a case described by Dr. Cayley under the title "Cirrhosis and Acute Atrophy of the Liver," and published in the 'Path. Soc. Trans.' for 1883, p. 127. The coloured diagram of the naked-eye appearance of the liver *post mortem* might have been drawn from the present specimen, so closely does it resemble it. The description of the microscopical appearance also corresponds. Clinically the history of the case is similar, with the exception that in his case there was an alcoholic history. The patient was a man aged 30 years who, two months before death, began to suffer with pain in the epigastrium, dyspepsia, and jaundice. The jaundice increased but was never very intense, and ascites set in a week or two before death. He gradually became weaker and delirious at night and lapsed into a state of coma, dying about two months

after the onset of symptoms. The temperature was subnormal, the urine did not contain leucin or tyrosin; there was no vomiting till a few days before death; the day before he died petechial hæmorrhages were present on the abdomen, and he vomited some blood. At the autopsy the liver weighed 35 oz., and in appearance resembled the present specimen. The only important difference in the *post-mortem* examination was that in Dr. Cayley's case numerous tubercular ulcers were present in the intestine, and tubercles were also present on the peritoneum. The acute onset and severe nature of the final symptoms led Dr. Cayley to classify it as a case of acute atrophy supervening on a chronic condition.

The next case (Case 3) is that of an old woman, aged 73 years, who was admitted to St. Mary's Hospital for jaundice of six weeks' duration.

On admission she was semi-comatose, pulse 132, temp. 101·8° F. Tongue coated. Urine: s. g., 1025, no albumen.

She got rapidly worse and became comatose and unconscious, dying three days after admission.

Unfortunately, no history could be obtained of her mode of life or previous illness.

At the autopsy the liver was found to be very small, weighing only 28 oz. The capsule was puckered and wrinkled, but not hobnail. On section, islands of bile-stained fatty liver cells were seen dotted about in a bed of opaque hard fibrous tissue, with hæmorrhages in places. There were no gall-stones, and there was no obvious obstruction of the larger bile-ducts. The spleen was large and fibrous; the kidneys weighed 5½ oz.; the capsule stripped, leaving a somewhat granular surface.

Kidney.—Microscopically there was extreme hyaline degeneration of the glomeruli, with atrophy of renal epithelium and interstitial fibrosis.

Liver.—Microscopically the liver substance is largely replaced by a coarse reticulum of fibrous tissue, which is most dense in the neighbourhood of the portal canals. Here and there in these tracts of fibrous tissue are large hæmorrhages. The liver-cells occur in islands, and in many of them the nuclei stain well, and the cells have their normal shape and outline and do not appear to have suffered much damage. Others are in an advanced state of fatty degeneration, or have entirely disappeared.

The next case (Case 4) is that of a girl, aged 12 years, admitted to St. Mary's Hospital under Dr. Lees, in August, 1904. The history was that she was suddenly taken ill in the night of August 5th, five days before admission, when she woke up and clutched her mother in a fright and shortly afterwards vomited. The vomiting persisted and she became jaundiced and very restless. The day before admission she had a rigor and became semi-comatose. On admission she was slightly jaundiced and lay on her back, scarcely conscious of her surroundings. The next day the temperature rose to 101·2° and there were spasmodic twitchings of the right arm and leg, suggestive of an irritative cerebral lesion. She was accordingly trephined over the left motor cortex, but nothing abnormal was found and she died shortly after the operation. At the autopsy the liver was very small, weighing only 14 oz. The capsule was not thickened but was for the most part smooth, with irregular elevations in places, which on section were seen to be small islands of yellow bile-stained liver-cells embedded in a ground-work of fibrous tissue. The distribution of the fibrous tissue is irregular, and parts of the liver appear to be normal to the naked eye. The brain was normal and there was no meningitis. Microscopically there are large tracts of fibrous tissue, with numerous bile-ducts and areas of round-celled infiltration, in which are seen groups of liver-cells, some in an advanced stage of fatty degeneration, others almost normal in appearance. There were no gall-stones and there was no obstruction in the larger bile-ducts.

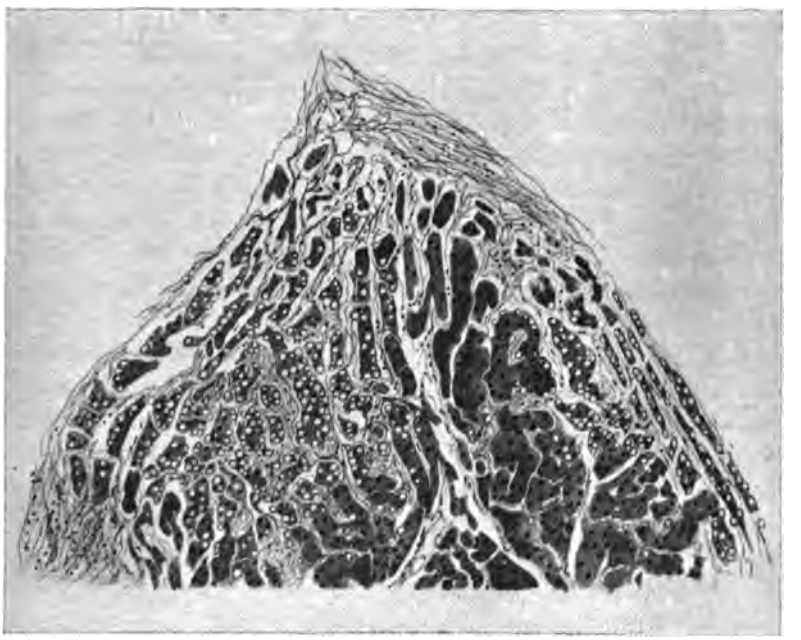
I have here also on the table a liver which might represent a more advanced stage of the disease as seen in this last case. The left lobe is entirely converted into dense fibrous tissue; in the right lobe groups of liver-cells in a state of fatty degeneration are seen embedded in fibrous tissue, which in places is very dense and extensive and is devoid of liver-cells.

This liver was from a boy, aged 6 years, who had been ailing 16 months, and two weeks before admission was taken ill with pain in the abdomen and vomiting. He became restless, his temperature rose to 101°; there was twitching of the limbs and there were cerebral symptoms suggestive of meningitis, with delirium, lapsing into coma. The clinical history of this case was, therefore, strikingly similar to that of the last in the sudden and acute onset of the final symptoms. There was in this case, how-

ever, a history of congenital syphilis, in which condition a diffuse fine fibrosis is not uncommon.

The pathological appearance of the liver in these five cases is that of a diffuse interstitial fibrosis with great destruction of the liver-cells. Clinically the final stage in each was characterised by the abrupt onset of severe symptoms, with pyrexia, terminating in delirium and coma. In three cases jaundice was present, and in two ascites set in some weeks before admission; but in the last two cases described there were no severe symptoms till eight and

FIG. 36.



Section of liver from Case 4, showing fatty degeneration of the liver-cells, strands of newly formed fibrous tissue, and recent cellular proliferation.

fourteen days before death respectively. The sudden onset and acute nature of the final symptoms are puzzling. They may have been due to the supervention of an acute infection, or possibly to the entrance into the general systemic circulation of products from the intestine imperfectly metabolised by the damaged liver, the remaining cells of which were so reduced or incapacitated that they struck work suddenly, being unable to transform the contents of the portal vein into material suitable for the systemic circulation

The etiology of the interstitial hepatitis or cirrhosis is obscure. There was no history of alcohol or syphilis, except in the last case, but the pathological appearances suggest some toxæmia, the stress of which fell primarily on the liver.

The question arises (1) as to the channel through which the toxin or infective agent was conveyed to the liver; (2) as to the nature of the toxin.

The channels through which toxins may have access to the liver are: (1) The biliary canals; (2) the hepatic artery; (3) the portal vein.

It is claimed that obstruction in the biliary canals may produce cirrhosis, but, experimentally, ligature of the bile-duct does not give rise to cirrhosis except in small localised areas, and in cases of prolonged and extreme biliary obstruction, such as is often produced by carcinoma of the head of the pancreas occluding the common bile-duct, I have never seen cirrhosis result.

One way in which it seems possible for the inflammatory lesions of the liver to result from biliary obstruction is by infection of stagnant bile from the intestine, such as may occur when a gall-stone is lodged in the common bile-duct and ulceration takes place.

In three such cases I have obtained a culture of *B. coli* from the bile, and have demonstrated the *B. coli* in the biliary capillaries in suitably stained sections. The infection was, however, acute, and the patients died from suppurative cholangitis. Possibly with a less virulent infection a true biliary cirrhosis might result. In the cases under review there was no history of gall-stones and no obstruction of the common bile-duct, and cultures from the bile were sterile.

It is conceivable in a general toxæmia due to a constitutional disorder of bacterial origin, that toxins reaching the liver through the hepatic artery should set up inflammatory reaction in the neighbourhood of its capillaries.

Claude, in 1897, published a thesis on the lesions in the liver and kidneys produced by experimental inoculation of animals with various toxins, namely of *B. coli*, the diphtheria bacillus, Streptococcus and Staphylococcus pyogenes, and pyocyaneus. He found that large doses of toxin, which caused the death of the animal in one to three days, produced cloudy swelling and fatty degeneration of the liver-cells; small doses of the toxin,

repeated at intervals, produced peri- and endarteritis of the arterioles of the hepatic artery, with round-celled exudation and proliferation of connective-tissue cells in their neighbourhood, and some degenerative changes in the liver-cells at the periphery and towards the centre of the lobule. The lesions were more pronounced and extensive in the kidneys, as one might expect, inasmuch as they play the most important part in the elimination of toxins from the systemic circulation. One must not forget, however, that toxins present in the systemic circulation must necessarily be present in the portal vein as well as in the hepatic artery, and that they may have an injurious effect on the liver-cells, causing the death of some, which in the event of recovery may be replaced by fibrous tissue derived from proliferated connective-tissue cells in the portal canals.

In one of the cases (Case 2) under discussion there was a history of some acute illness, stated to be "influenza," nine months previously, from which the patient never seemed quite to recover. Jaundice and ascites set in some months after, and were persistent. It is conceivable that a widespread destruction of liver-cells took place during the acute illness, and that they were replaced by a new formation of fibrous tissue, which as it contracted caused obstruction to the biliary canals and branches of the portal vein, with resulting jaundice and ascites.

I have here a liver from a girl who died of acute pneumonia, which shows an area of sub-capsular fatty degeneration about one and a half inches in diameter and a quarter of an inch thick, and several smaller similar areas. Such areas of localised subcapsular fatty degeneration, and also similar diffuse irregular areas of fatty degeneration in the deeper parts of the liver, are not uncommon in acute toxæmias. Microscopic examination shows complete cell destruction in these areas, and in event of recovery it is possible that cicatrisation of such areas may be the starting-point of a diffuse cirrhosis.

I have here also a microscopic section from the liver of a man who died of malignant endocarditis after two previous attacks of rheumatism. This shows some old fibrosis and recent cell destruction, with numerous hæmorrhages and extreme congestion. In such a case, in the event of recovery, the process of repair would necessarily be attended by the formation of much new fibrous tissue.

In a discussion on cirrhosis of the liver at the meeting of the British Medical Association, 1900,[1] Flexner described some experiments in which, by the inoculation of ricin and abrin into rabbits, he had, with large doses, produced cell destruction and necrosis without proliferative changes in the connective tissue, while with smaller repeated doses there was formation of new fibrous tissue and proliferation of the bile-ducts, suggestive of atrophic cirrhosis.

Lazarus Barlow[2] held the view that cell destruction precedes fibrosis, and that the latter is an attempt on the part of the connective-tissue cells to repair the lacunæ resulting from cell destruction.

With this view I am in accord, and it seems only natural that toxins conveyed by the portal vein should cause destruction of the cells which it supplies and amongst which its capillaries run. The connective tissue in the liver and the bile-ducts, being nourished by the hepatic artery, would not be directly affected by toxins in the portal vein; but when cell destruction has taken place and the toxins are liberated in the neighbourhood of the connective tissue, it is in accordance with Nature's principles that an attempt should be made to resist the invasion and repair the damage by proliferation of fibroblasts and formation of new fibrous tissue. In the liver it would seem that proliferation of bile-ducts is also a part of the process. The new-formed fibrous tissue as it contracts would tend to damage the liver still further, and possibly cause atrophy of some of the previously undamaged cells.

When we come to the question as to the nature of the toxins the subject is one of great difficulty. In children and young adults we meet with a large number of cases of cirrhosis in which none of the commonly recognised causes in adults can be incriminated.

Palmer Howard,[3] of Montreal, published in 1887 a paper on "Hepatic Cirrhoses in Children," of which he had collected sixty-two cases. In less than half of these was there any clue to their etiology. In ten there was a possibility of alcohol, injudiciously administered, being the cause; in seven there was a history of congenital syphilis; in nine there was a history of scarlet fever

[1] 'Brit. Med. Journ.,' 1900, p. 913.
[2] Ibid., p. 914.
[3] Howard, 'Trans. Amer. Phys.,' vol. ii, 1887.

or measles; and in seven of tuberculosis, but in a large number no accurate history of previous illness was obtainable. In 1887 Klein described interstitial hepatitis as present in eight cases of scarlet fever which he had investigated. I think it possible, therefore, that many cases of unexplained cirrhosis of the liver may have their origin in some previous acute specific disease or infection of bacterial origin.

I have examined the kidneys in a large number of cases of cirrhosis of the liver of undoubted alcoholic origin, and have been struck by the comparative rarity of any severe lesions of the kidneys when the liver is extensively diseased. It is, perhaps, what one might expect, as the stress of toxins absorbed from the intestinal canal would naturally fall on the liver-cells, one of whose functions is to render the blood conveyed to them by the portal vein suitable for the systemic circulation, whereas the kidneys are the chief eliminators of toxins from the systemic circulation.

It occurred to me that microscopic examination of the kidney in cases of cirrhosis might afford some clue as to whether the cirrhosis was the result of toxins derived from the intestinal canal, or of toxins present in the portal vein as the result of a general toxæmia due to a bacterial infection; in the latter case one would expect to find the kidneys diseased as well. I have not, however, been able to come to any conclusion on this point, as the toxins are so many and varied and may differ widely in their action on different tissues.

The question as to the nature of toxins derived from the alimentary canal is one of great difficulty, as with the exclusion of alcohol and certain metallic poisons such as arsenic and lead, we have to fall back on toxins derived from bacterial fermentation, or imperfect digestion of food products, or lesions in the wall of the intestines. Boix found that acetic acid and to a less degree butyric and lactic acids administered daily in small doses to a rabbit produced cirrhosis and fatty degeneration of the liver-cells, and it may be that gastro-intestinal disorders leading to the absorption of imperfectly metabolised ingesta or toxic substances generated in the intestinal canal are a common cause of cirrhosis of the liver.

It would not be so remarkable to find cirrhosis and other disorders of the liver resulting from the rich and variegated diet of the wealthy classes, but the cases under review, and a large

proportion of the cases of cirrhosis in children quoted by Palmer Howard, occurred in subjects who could not afford any luxuries or delicacies in diet.

CONCLUSIONS.

(1) Toxæmic jaundice or acute yellow atrophy is due to toxins, ingested or generated in the intestinal canal, or possibly the result of an acute bacterial infection, the virulence of which is such that it causes a rapid and widespread destruction of liver-cells, and death occurs without any attempt at repair or cell proliferation.

(2) Cirrhosis of the liver is due to toxins of less virulence and more prolonged duration, which cause gradual and patchy destruction of the liver-cells; these are replaced by proliferation of the connective-tissue cells and bile-ducts, with resulting new formation of fibrous tissue and bile-ducts. Subsequent cicatricial contraction of the newly formed fibrous tissue causes further deformity of the liver and cell atrophy.

(3) The causes of cirrhosis of the liver may be:—1, Ingested toxic substances such as alcohol and certain metallic poisons, *e. g.* lead; 2, Toxins generated in the intestinal canal as the result of imperfect digestion or bacterial fermentation; 3, Certain constitutional disorders, *e. g.* syphilis. It is also probable that specific fevers and prolonged bacterial infections may give rise to cell destruction and subsequent fibrosis or cirrhosis of the liver in subjects in whom the liver is unusually susceptible, more especially in children and young adults.

October 18*th*, 1904.

15. *Recent work on proteid chemistry.*

By W. D. HALLIBURTON, F.R.S.

THE extreme importance which the study of proteid chemistry has attained will, I feel, justify its selection for a review, although I fear that so complex a subject cannot be adequately treated in a paper of limited extent; seeing, also, that much of the apparent complexity of the subject arises from its technicalities, I propose to deal with it in its main outlines, and to avoid as far as possible complications of a purely technical nature.

The chemical constitution of the proteid molecule is still for the future. Chemists and physiologists alike for long fought shy of any attempts to unravel its mysteries. But by degrees the puzzle is being solved; many of the proteids can now be prepared in a pure—that is, crystalline—form; the simplest proteids, the protamines, are yielding their secrets to Kossel and his co-workers. Emil Fischer also has brought his great experience to bear on the problem, and interesting announcements from him appear from time to time, and are eagerly expected in the future.

When this great conquest of organic chemistry is accomplished

physiologists and pathologists alike will be furnished with new light on many of the dark spots in their knowledge.

Before it is possible for chemists to attempt a synthesis of the proteid molecule, an obvious and preliminary necessity is a correct knowledge of its analytical cleavage products.

One of the most instructive methods of accomplishing the breakdown is by means of proteolytic ferments. According to the doctrine of Kühne, gastric as well as tryptic digestion leads to the formation, first of primary proteoses or albumoses; these are then broken up into secondary proteoses, and these in turn into the still smaller molecules of peptone. He further differentiated between the peptone produced in the stomach and that produced during pancreatic digestion. The peptone produced in the stomach he termed "amphopeptone," which he considered consists of two hypothetical groups united together; of these two groups one "hemipeptone" can be further decomposed by trypsin into still simpler materials, whilst the other, antipeptone, is resistant. According to this view, tryptic digestion thus leads to the formation of an antipeptone, which differs from the amphopeptone of peptic digestion in the absence of the hemi-complexes, these having been decomposed with the formation of amino-acids.

This conception has been modified by recent investigation. Through the Strassburg School in particular it has been shown that the number of primary products of peptic digestion is larger than Kühne supposed, and that in quite early stages in digestion substances are formed alongside of the albumoses, which no longer give typical proteid reactions like the biuret reaction. The secondary or dentero-albumoses, which at a later stage are derived from the primary, are also numerous; following this stage, products are formed which differ from the albumoses in the fact that they cannot be precipitated by saturation with ammonium sulphate in either acid, alkaline, or neutral media. To these Kühne applied the term "peptone," but there is no doubt that the material labelled with this name does not wholly consist of small moleculed proteid matter, but mixed with it are substances which have passed beyond the peptone stage of cleavage, and differ from the peptones by no longer giving the biuret reaction. Kühne himself doubted the unity of antipeptone, and it has now been demonstrated that this substance is not a pep-

tone at all, but a mixture of simpler cleavage products of which various amino-acids and hexone bases have already been isolated and identified.

It has further been shown that there are no essential differences between the action of the gastric agent pepsin-hydrochloric acid and the pancreatic enzyme trypsin. The action of these proteolytic ferments, in other words, is by a process of hydrolysis to split the heavy proteid molecule into smaller and smaller molecules; first we get proteoses, then peptones, and, finally, simple products like leucine and tyrosine. A variable fraction of the proteid molecule is broken off with comparative ease, and the whole breakdown is more easily performed by the powerful tryptic enzyme than by the comparatively feeble agent pepsin-hydrochloric acid. The latter substance, however, is not entirely inactive in this direction; for although much leucine and tyrosine are not usually found in a peptic digest unless the action has been very prolonged, yet there is a little of these substances mixed with others of low molecular weight (aspartic acid, hexone bases, etc.) which were incorrectly grouped together by the earlier workers as a peptone, the anti-group of the amphopeptone complex. The difference between pepsin and trypsin is mainly one of velocity of action.

Ampho-peptone, hemi-peptone, and anti-peptone (in the original meaning of these words) do not exist, and with the destruction of the original conception of peptone interest centres in the final products. The greater number of these fall within the following groups:

(1) *The mono-amino acids*, such as glycine (amino-acetic acid), alanine (amino-propionic acid), leucine (amino-caproic acid), amino-valeric acid, asparagine (amino-succinamic acid), aspartic acid (amino-succinic acid), glutamic acid (amino-pyrotartaric acid).

(2) *The diamino acids*, such as ornithine (diamino-valeric acid), arginine (a compound of ornithine with a urea group), lysine (diamino-caproic acid). The introduction of a second amino group (NH_2) into fatty acids confers on them basic properties; hence arginine and lysine are often spoken of as hexone bases (hexone, because they contain six carbon atoms); the third member of the hexone base group, called "histidine," is probably of a corresponding nature.

(3) The aromatic amino acids, such as phenyl-alanine, tyrosine (oxy-phenyl-alanine), tryptophane (indole-amino propionic acid).

(4) In addition to the foregoing there are nitrogenous derivatives of the benzene ring (indole, scatole), pyrimidine bases (thymine, cytosine), pyrrolidine derivatives, the sulphur-containing substance cystin, and ammonia.

The foregoing list represents various nuclei which exist preformed in the proteid molecule, and are there linked in more or less complex groups. Such a list makes one realise the complicated nature of the proteid molecule, and the difficulties that fence around its investigation.

But Emil Fischer has begun at the right end; the first thing to do is obviously to make a complete list of the cleavage products and to unravel their constitution; the next is to find out how they are linked together in groups, and the last to accomplish the linkage of the groups themselves.

He has already discovered that during proteolysis some of these groups can be detected and separated, and the ones that have particularly attracted his attention are the combinations of amino-acids, which he has termed "polypeptides." Thus he has separated out, among others, two leucine radicles linked together (alanyl-leucine), glycine united to leucine (glycyl-leucine), glycyl-asparagine, alanyl-glycyl-leucine, and others containing the nuclei of aromatic amino-acids. The polypeptides are ultimately broken down into the amino-acids of which they are composed, and therefore occupy a position intermediate between the proteoses and peptones on the one hand and the final products on the other. The important fact we now come to is, that he has succeeded in making many of these polypeptides synthetically, and thus there is great promise of the work culminating in an actual synthesis of the proteid molecule.

I next pass from these purely chemical considerations to one important aspect of their physiological application. For simultaneously advances have been made in our knowledge of proteid absorption. It is not many years ago that leucine and tyrosine and substances of the same category were regarded as more or less waste material, due to the excessive action of pancreatic juice. We used to teach that the small fraction so broken off was hurried to the liver, and finally and rapidly converted into urea, and got rid of. They were never supposed to be built

into the living protoplasmic molecule. It was known that the absorptive epithelium of the intestine possessed the power of regenerating albumin from albumoses and peptones, but it was not suspected that the synthetic power of these cells was equal to a building up of proteid from quite simple cleavage products.

Evidence, however, is rapidly accumulating to show that this may possibly occur. During both gastric and intestinal digestion the albuminous molecule is much more completely broken down to its fundamental components than was considered to be the case by Kühne and his school. The intestinal juice contains a special ferment, erepsin, which decomposes the peptone into amino-acids and the like. The major part of the proteid ingested is now believed to undergo this extreme cleavage, and this being so, the various proteids of the body must be formed synthetically from comparatively simple materials. There is thus an analogy between what happens to proteids and what we already know happens to fat and carbohydrate. Fat during digestion is broken down into its fatty acids and glycerin; fat during absorption and assimilation is once more synthesised from these simple molecules. Starch during digestion is broken down into substances with smaller molecules. First the dextrins appear (analogous to albumoses and peptones); these are converted into molecules of maltose a disaccharide (analogous to the polypeptides) and finally the simple molecules of glucose are formed from this. Once more, on absorption and assimilation the heavy molecules of animal starch or glycogen are synthetically built from the small molecules of sugar.

Loewi and others, moreover, have shown by experiments on animals that it is possible to maintain their weight, health, and nitrogenous equilibrium for a considerable time by feeding them on the crystalline cleavage products resulting from pancreatic proteolysis, which no longer give the biuret reaction. We are thus presented with an entirely new conception regarding the origin of the most important chemical material of living substance.

I should add that it has not been possible as yet to discover in the blood-stream these cleavage products when they are administered by the alimentary canal, so that the building of them together is provisionally considered to occur in the absorptive epithelium of the alimentary tract.

I think you will agree with me that there is something attractive in a theory that assumes a complete breakdown of the foodstuffs previous to their being built up into living tissue. It is less difficult to understand how the living organism can construct from the fragments the tissues peculiar to itself, and maintain its chemical integrity although the food taken may vary widely in composition.

What, then, if this theory is true, would be the fate of food proteids introduced direct into the blood-stream without the intervention of the alimentary digestive processes. This is a question to which Mendel and Rockwood [1] have been attempting to find an answer. If the preliminary cleavage in the gastro-intestinal tract is absolutely necessary, one would anticipate that a foreign food proteid (such as vegetable proteid) administered by intravenous or intra-peritoneal injection would not be assimilated, but would be cast out of the body in one or more of the excretions. But Mendel and Rockwood found that they are not eliminated unchanged in either urine or bile. In some cases a proteose is found in small quantities in the urine, but the greater part of the proteid administered is retained in the body, especially if the injection is slowly performed. Rapid injection causes toxic symptoms, as one would anticipate. It would be interesting to ascertain something further regarding what happens to the retained proteid and the exact mode of utilisation which it undergoes. No doubt future attempts will be made in this direction. The fact that proteids are retained after this method of administration and apparently utilised does not really militate against the theory that proteids are under normal circumstances more or less completely broken down in the alimentary tract. Clinical experience with nutrient enemata indicates the possibility of a direct absorption of proteid without previous digestive changes. We have here one of many instances of the adaptability of the body to altered circumstances; at a push various portions of the body are capable of rising to the occasion and performing unusual feats, or of taking on the action normally carried out elsewhere. The usual form in which the body gets its proteid is by building it up from simple crystalline materials, but if these are not available it still can get proteid by absorbing the large molecules of the albumin presented

[1] 'Amer Journ. of Physiol.,' vol. xii, p. 336, 1905.

to it. It is possible that if cleavage is absolutely necessary, the cells of other tissues, or the enzymes present in those cells are capable of vicariously taking the place of trypsin and intestinal erepsin and doing their work. The presence of a proteose in urine in some of Mendel and Rockwood's experiments points in this direction, and this view is supported by Vernon's recent discovery that every tissue of the body has an ereptic action, and in some cases (*e. g.* the kidney) this power is greater than in the intestinal cavity and mucous membrane.

The mention of tissue erepsins leads me next to speak in general terms of the process of autolysis. By this one means that an organ removed from the body and kept sterile at a suitable temperature will in time digest itself. The study of autolysis has up to the present been mainly concerned with the subject of auto-digestion of proteids and nucleo-proteids. I have recently had to prepare a summary of the bio-chemical researches of last year, and I have been immensely struck with the large number of papers which deal with this subject. I will not trouble you with a list of them; there can, however, be no doubt that the activity manifested by so many workers is warranted by the importance of the subject. The tissue enzymes are important in the metabolic cycle during life; they probably enable the tissue-cells to break down and then assimilate the proteids brought to them *viâ* blood and lymph, as well as to initiate the subsequent katabolic changes which terminate in excretion of waste materials. Before it is possible to state what the function of such enzymes are during life, it is necessary to study what happens when they are allowed full scope after death. The curious thing about such enzymes is that the majority act best in an acid medium, whereas the healthy tissues during life are alkaline. There is, however, no difficulty in supposing there are temporary phases of acidity, or acid foci, in living cells, although the reaction of the mass of the tissue to the ordinary indicators may be alkaline. There is, further, no doubt that the nuclei of cells are the main centres for nutritional exchange, and so especial interest attaches to the results of autolysis of nucleo-proteids. Here it is found that the end products often differ markedly from those which result from hydrolysis by acids, and so Jones and Partridge searched for and found certain specific enzymes which account for the differ-

ence. The pancreas, when subjected to autolysis, does not yield adenine or guanine, and if guanine is added to it, it is rapidly transformed into xanthine; the name *guanase* is bestowed on the enzyme to which this change is due. Another enzyme, *adenase*, found especially in the spleen, in a similar way converts adenine into hypoxanthine.

The search for such ferments acting on comparatively simple materials was, no doubt, the direct result of the striking and suggestive work of Kossel and Dakin which led them to the discovery of *arginase*. Arginase splits arginine almost quantitatively into urea and ornithine. The failure of some observers to find arginine in the products of auto-digestion of organs is due to the previously unsuspected action of arginase, which must be placed among Richet's urea-forming ferments. Arginase is found in many parts, but is not universally distributed in all tissues; it is most abundant in the liver, the principal urea-forming organ. We therefore see that a study of autolysis has already had the important practical issue of enabling us to obtain a little deeper insight into the metabolic processes that lead to urea formation.

Any paper dealing with recent works on the proteids in relation to diet would be incomplete without a reference to Prof. Chittenden's just published book on 'Physiological Economy in Nutrition.' The long-established idea that a man requires a minimum of 15 to 18 grammes of nitrogen in his daily food has been for some time past seriously questioned. This is a number based roughly on the usual diet of the meat-eating nations, and it is argued that habit and instinct alike are safe guides in determining such a number, and that the effects of such a diet in the maintenance of health and equilibrium has been abundantly proved through centuries of experience. It is the number which forms the basis of the usually accepted dietaries of Ranke and Voit.

In other nationalities, it is true, a different figure has been arrived at as the result of experience and instinct. Thus in certain semi-civilised races, the proportion of flesh food is much larger, and in other races again—and this is a commoner variation —the proteid intake is less. I do not suppose anyone will advocate a return to more carnivorous habits; we need, therefore, only consider the second alternative. It is alleged that in such

nationalities as the Japanese, or in groups of people like vegetarians, and in many rural populations, health and equilibrium are as equally well maintained as in the ordinary meat-eating inhabitants of our large cities. Those who hold that the number fifteen to eighteen is the correct one have explained the different number arrived at by the nations of the Far East as a racial difference propagated by long centuries of inheritance, or have tried more or less successfully to show that such people come nearer to Voit's standard than had been supposed, or that they are not properly nourished.

Such explanations will not hold water when applied to the experiments conducted by Professor Chittenden upon himself, his colleagues, his students, and upon athletes and soldiers. These experiments lasted in all cases for months, in some for more than a year. The proteid intake was reduced to half, and in some cases to less than half the number regarded as normal. After a variable initial drop in body weight, the deprivation was apparently followed by no untoward results. Equilibrium was maintained; the health remained perfect or improved; the muscular force in athletes was usually increased; mental acuity was undiminished, and desire for richer food disappeared.

The question was brought to the front by Mr. Horace Fletcher, who states that he cured himself of dyspeptic troubles by lessening his proteid nutriment below what was regarded as the physiological standard. He has started a propaganda on the subject from the economic point of view, and one at once sees its immense importance from this standpoint, as well as from that of the physiological investigator and dietician. Mr. Fletcher attributed great importance to a thorough mastication of the food; mastication, of course, is important, but it will not explain the results of the experiments made by Chittenden and his fellow-workers.

Chittenden argues from his work (and the details of his experiments will amply repay perusal) that his scanty proteid diet is the normal, and that the average meat-eater is the man who is abnormal. He says: "When we recollect that these eighteen grammes or more of nitrogen in the urine reach the final stage of urea, etc., only by passing through a series of stages, each one of which means the using up of a certain amount of energy, to say nothing of the energy made use of in digestion, absorption, etc., we can easily picture to ourselves the amount of physio-

logical labour which the daily handling by the body of such amounts of proteid food entails. It needs very little imagination to see that a large amount of energy is used up in passing on these nitrogenous waste products from organ to organ, or from tissue to tissue, on the way to elimination, and we can fancy that liver and kidneys must at times rebel at the excessive labour they are called upon to perform." He then goes on to point out how many of the nitrogenous katabolites are toxic, and the evil results due to their accumulation. He continues: "If it is true that a daily intake of 118 grammes of proteid food more or less is necessary, then we must consider that the good overbalances the evil. But we are certainly justified on the basis of our daily observations on a large number of individuals, and extending over many months, in saying that there is no apparent need for any such amount of proteid food as is ordinarily consumed by the average individual."

Chittenden advocates a revolution in our ordinary dietary, and his arguments for temperance in proteid intake are advanced in a temperate manner, the *pros* and *cons* being considered as a scientific man would be expected to consider them.

I shall doubtless be asked if I am convinced, and if I am prepared to support Chittenden's views. But the question is not so simple as it appears at first sight, and an habitually cautious person may be excused if he refrains from a positive expression of opinion at present. One would, for instance, like to know whether the numerous subjects of the experiments are still keeping up their reduced diet, or whether they have returned to the flesh-pots after a period of enforced abstinence. If they are still maintaining their new habits, one would like to know how they fare in a few years' time, if they have the reserve force to enable them to withstand a severe disease, great fatigue, and severe privation—for instance, during a siege, and whether the initial briskness they felt when they dropped their large (probably too large) proteid intake, is maintained, or whether, on the other hand, they present the appearance and symptoms of underfed persons.

One can realise the different ways in which different people will receive such a book as Chittenden's. There is the enthusiastic reformer, who will welcome it with open arms. There is the easily persuaded person, always ready to accept the last

new thing he has read without question; he also will, for a time at least, pin his faith to the new principle in dietetics. There is the ultra-conservative, who detests new things and new ideas, and will probably think he has settled the matter by calling Chittenden a crank or a faddist. There is the *bon vivant*, who will resent any interference with his habits, gout and other evils notwithstanding; and there is the vast mass of people who will take no notice of the matter at all. None of these need concern us. But in addition to all these there is the honest enquirer, ready to be convinced on sufficient evidence, but withholding his opinion until the testimony is overwhelming. Such an individual would point to the danger of a sudden change in the habits of years and of generations, even although it may ultimately be necessary. He may recall the analogy of metabolic changes to commercial undertakings which physiologists so often employ when presenting balance-sheets of intake and output, and say that just as in a commercial enterprise a large turnover implies healthy activity, so in the body a frequent exchange of the old for the new is within certain limits an indication of vigour, and a necessary accompaniment of healthy action. He may point to the liver, the largest organ we possess, whose function it is to turn nitrogenous metabolites which may be harmful into urea, which is harmless and easily disposed of; the organ is adequately large and active in health to deal with large quantities of material. He may point around him to the stunted and feeble inhabitants among the poor and ask why they are so. Unhealthy dwellings, excess of alcohol, insufficiency of light and of pure air will explain a good deal of their condition, but is it not underfeeding which is at the root of the matter? They have had, *nolens volens*, to subsist on a diet very like Chittenden's; but their nutritive condition is not such as to make people who can afford a more liberal table inclined to follow their example. He will ask, Why is it that with few exceptions the meat-eating nations have risen to the front? and Why is it that in countries (*e. g.* in the East) where the native population is diluted with the white races it is the former who are more readily attacked by disease, and more easily succumb to its effects?

All these points of view, all these difficulties, must be met, and there is one more question which, perhaps, is the most important of all, and which the recent researches of Chittenden

have not touched, and that is the question of infant feeding. The diet of the child is relatively far richer in proteid than that of the adult. Must we also reduce the intake of proteid food in the growing child? Clinical experience does not point, so far as I can ascertain, to an affirmative answer, either with regard to the feeding of infants or of certain classes of invalids.

I have not put these questions for the purpose of answering them myself; I am not an advocate on the anti-Chittenden side, but I am merely showing that there are difficulties, and serious ones, which will have to be answered before the advocacy of a new idea will meet with success.

One more point and I have done. The question of What is a normal diet? is intimately bound up with another, and that is, What is a normal urine? This question is dealt with in two most interesting papers which have appeared from another American centre of work by Otto Folin.[1] The text-book statements are all derived from the examination of the urine of people accustomed to the Voit dietary; but if the diet of the future is to contain only half as much proteid, the urine of the future will naturally show a nitrogenous output of half of what is now regarded as normal. In people on such reduced diets Folin shows that the decrease in urinary nitrogen falls mainly on the urea fraction, and in some cases the urea excreted accounted for only 66 per cent. of the total nitrogen. The other nitrogenous katabolites of the urine alter comparatively little absolutely; but relatively, their amount rises; of these the endogenous purine, and more particularly the creatinine remain remarkably constant in absolute amount in spite of the great reduction in the proteid ingested.

It is impossible, however, to summarise these two long and important papers in half a dozen lines, but it would lead me beyond the object of this paper to treat the subject more fully.

What I have endeavoured to do is, not to make an exhaustive survey of all the recent literature in connection with the proteids, or even to allude to many of the by-paths which branch off from the main track. Those of my listeners who are pathologists will, for instance, recognise the importance of the question in reference to immunity and allied problems. Before, however, it

[1] 'Amer. Journ. of Physiol.,' vol. xiii, 1905, pp. 45-65, 66-115.

is possible to understand those small but important differences which make one proteid a food and another a poison, or distinguish the serum proteids of one animal from those of another, it is necessary to clear the way by obtaining the answer to the still unsolved question of the constitution of the proteids generally, the manner of their synthesis *in vitro* and *in vivo*, and the exact *rôle* they play in ordinary metabolism.

March 7th, 1905.

Addendum.

SINCE the foregoing was written, a third paper by O. Folin has appeared on theories of proteid-metabolism ('Amer. Journ. Physiol.,' xiii, 117, 1905). In it he continues the line of argument started by his work on the urine, for the laws governing the composition of urine are the effect of more fundamental laws governing proteid-katabolism. Voit's theory states that katabolism occurs only in the "circulating proteid." The small amount of "living proteid" which dies is dissolved, and is so added to the circulating proteid. Pflüger, on the other hand, believes that all proteid is first transformed into living material before katabolism occurs. The view taken by Folin is that neither of these extreme views is correct, but that nitrogenous katabolism is of two kinds; one is inconstant and immediate, varies with the food, and leads to the formation of urea and inorganic sulphates, but not of creatinine, or "neutral sulphur." The other is smaller in amount, constant in quantity, and is largely represented by creatinine, neutral sulphur, and, to a less extent, by uric acid and ethereal sulphates, and possibly a certain amount of urea. The latter form of metabolism may be termed tissue, or *endogenous* metabolism, whilst the other is *exogenous*. Endogenous metabolism sets a limit to the lowest level of nitrogenous equilibrium attainable. The proteid sufficient to maintain endogenous katabolism is indispensable; whether the amount exogenously katabolised can be entirely dispensed with is at present questionable, but there is evidence to show that it can largely be replaced by non-nitrogenous food; the nitrogen is easily split off by hydrolysis without oxidation, and thus a non-nitrogenous residue remains available for calorific processes. Urea is absent from the muscles, and its representa-

tive creatine is eliminated not as urea, but as creatinine. The katabolism that terminates in urea formation is not of such fundamental importance as that which leads to the elimination of creatinine. The formation of ammonia and amino-acids which occurs so largely in the intestine owing to tryptic and ereptic activity is probably a preliminary means of getting rid of the excess of nitrogen taken in. The evidence that these simple materials are synthesised into tissue-proteids is certainly inconclusive and largely teleological; the formation of urea direct from them by the liver is more probable. The hypothesis that the organism uses proteid if it can get it, even when fats and carbohydrates are abundant, is also considered to be an unproved assumption. The well-established fact that the organism tends to maintain nitrogenous equilibrium within tremendously wide limits is inconsistent with the teleological argument of albumin formation. An extensive formation of Voit's circulating proteid to be followed immediately by decomposition into urea is quite as improbable as the corresponding formation and decomposition of Pflüger's organised protoplasm.

The organism requires in its food only the small amount of nitrogen necessary for endogenous metabolism; the nitrogen of the extra proteid is unnecessary, and the organism has at hand an active mechanism for immediately casting it out.

In carnivorous animals the uncertainty of the food supply has led to the development of a capacity to store a proteid reserve in the form of increased muscle substance, but in man this does not exist. Still that does not mean that the human organism can only replace lost muscle tissue slowly and with difficulty, for in convalescence from disease recovery of weight is astonishingly rapid. The 118 grammes per diem of proteid in standard diets is most excessive, and should largely be replaced by carbohydrates. The argument that most people take as much is of no real value, and might be equally well applied to the daily use of alcohol. The argument that nitrogenous equilibrium cannot be maintained for long periods on less has been disproved, notably by the recent work of Chittenden. In disease, where the presence of excess of waste is likely to be more harmful than in health, it is recommended that the intake of nitrogen should be limited to the level of the endogenous requirement (3 to 4 gram. daily). The fact that muscular work

does not increase proteid katabolism is remarkable if current views on the nature of that katabolism are correct, but it becomes intelligible if proteid katabolism, in so far as its nitrogen is concerned, is independent of the oxidations which give rise to heat or to the energy that is converted into work. Whether severe work will have an effect on the endogenous metabolism cannot be shown by investigating urea excretion; determinations of creatinine and neutral sulphur are necessary for a study of that question. *April 15th*, 1905.

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16. *The parasites of smallpox, vaccinia, and varicella.*

By W. E. de Korté.

(From the Bacteriological Laboratory, King's College, London.)

In attempting to ascertain the cause of amaas or Kaffir milk-pox it was hoped that if the morbific agent of that disease could be established light might be thrown on the cause of the analogous eruptive fever of smallpox. But all attempts to separate a specific organism for amaas proved as fruitless as have hitherto been all efforts to separate the agent of variola. That the specific cause or causes of variola, vaccinia, and amaas are in their respective lymphs is manifest. How, then, can the fact that so many capable observers have failed to detect the contagium in the vesicular contents of those diseases be accounted for? Three possible explanations suggest themselves in this connection. First, the organism may from the smallness of its dimensions escape detection. Chauveau, in his original investigation of calf lymph, clearly proves that the contagium of vaccinia is due to visible particles and that the elimination of these particles removes the effectiveness of vaccine lymph. The assumption that the cause of vaccinia is microscopically invisible is therefore not tenable. Secondly, the failure to recognise the germ may arise from the lack of a staining reaction which would serve to differentiate the pathogenic organism of variola or vaccinia from the *débris* present along with the organism in the pock. A third cause for the want of success in demonstrating the causal agent of variola or vaccinia by the methods usually adopted may be

that, on account of its fragile nature, the ordinary methods of staining and fixing invariably lead to its destruction. Fortunately, this third hypothesis is one which could easily be tested, and its disregard is, as I hope to prove, the reason why the arduous labours of many investigators have failed to bring to light the contagium vivum of variola and vaccinia.

With the object of testing this view of the case a hanging-drop preparation was made of amaas lymph which had been stored in the capillary tube for six months, no other manipulation beyond that of allowing the lymph to gravitate out of the tube on to the cover-slip being employed. On examination this specimen was seen to contain a large number of circular elements, a few of them showing a rounded nucleus, and including numbers of highly refractile granules in their interior. A number of these bodies were next seen to rupture and to disappear from view, a mass of granular detritus replacing them. This disruption, as was subsequently discovered, was due to desiccation, an agency infallibly destructive to the cellular element. The fact that these bodies had survived for six months in a capillary tube renders the possibility of their being leucocytes improbable (leucocytes in human blister fluid disappear, even though kept at the temperature of the blood, after 14 days); nor were they ordinary pus corpuscles, for in whatsoever manner fixation was attempted, whether by heat, alcohol and ether, or osmic acid, their destruction always resulted. Through the courtesy of Mr. E. C. Greenwood, Public Vaccinator for Marylebone, some human vaccine lymph was collected in capillary tubes on the ninth day of the disease. Put up as a hanging drop, with the same avoidance of manipulation as in the case of the amaas matter, this lymph also displayed a considerable number of unicellular globes with refractile contents. On the warm stage at 98° F. these bodies evinced considerable motility, the movements being so rapid at times that the alterations of shape could not be depicted. To make sure of encountering these bodies human vaccine lymph must be gathered on the eighth or ninth day of the eruption, at any rate not later than the ninth day, and should be examined within twenty-four hours of its collection, for it has been found that these cells disappear from the lymph spontaneously on or about the tenth day, whether situated in the vaccinia vesicle or stored in a capillary tube.

Leucocytes in human blister fluid kept at the temperature of the body may remain intact for five days or longer. For these reasons I consider these bodies to be protozoan parasites, though to what class of protozoa they belong I cannot say, but they are clearly not bacteria. Further evidence of their protozoan nature will be submitted later. The parasite is found in secondary vaccination as well as primary cases, though more abundantly in the latter. As there are comparatively few protozoa present in any given specimen of human vaccine lymph, it is advisable to centrifugalise the capillary tube containing it, and thus concentrate the parasites prior to examining the specimen. Should the drop exuded from the capillary tube be too deep, it may be spread with the edge of a small bit of paper after the manner of a blood-film, but owing to the extreme delicacy of the organism great care should be exercised to avoid its rupture by pressure or by desiccation. Should, however, variolous matter be available, the protozoon will be found in extraordinary numbers in the lymph from a pock on the fifth day of the eruption. Owing to the want of opportunity it has not been decided at what period the fully grown parasite makes its appearance in the pock.

From variolous matter stored in a capillary tube and free from any contaminating organism the protozoon can be regained six months after its collection and probably longer. To observe the parasite in glycerinated calf lymph—and all remarks refer to the glycerinated product—it is advisable to obtain fresh material, the fresher the better. A drop is allowed to exude on to a cover-slip from the capillary tube and then the drop is carefully spread with the edge of another cover-slip. By practice a certain thickness of smear will be found to yield the best results as to the number and visibility of the protozoon and also numerous refractile granules which I regard as its spores, both being present in large numbers, just in proportion to the virulence of the lymph; better results are obtained by suspending a small quantity of the lymph in normal saline solution.

The protozoon of variola and vaccinia.—For descriptive purposes I propose the temporary name of "amœba variolæ vel vacciniæ" for this protozoon. The fully developed parasite is an amœboid organism and measures about $\frac{1}{25000}$ of an inch and has for the most part an oblate spheroidal shape, but encysted forms are found in variolous matter and calf lymph which are four or five

times as large as this. The parasite consists essentially of cytoplasm, which in the encysted form is enclosed in a well-marked cell wall, and of a rounded or ovoid nucleus apparently having a definite membrane, and this nucleus can be seen to possess a circular nucleolus. The protoplasm of the cell is finely granular and contains large numbers of highly refractile greenish particles which I regard as the spores. The cytoplasm is divided into ectoplasm and endoplasm, the distinction being best seen when the organism is active. The nucleus cannot often be seen, being usually centrally situated and thus hidden by the numerous granules or spores contained in the cytoplasm. The spores give the amœba its characteristic appearance. It is difficult to be sure of the shape of the spore; in its earliest stage it would seem to be somewhat pyriform in outline, the thin end being probably continued into a flagellum, for the spore is exceedingly active immediately after its escape from the parent cell; its movement ceases at the temperature of the air, but recommences at blood heat. There are no vacuoles in the cytoplasm. No multiplication has as yet been seen to occur by direct division of the amœba nor has any phenomenon, beyond the embracing of one amœba by another, which could be interpreted as a sexual act, been observed.

The most characteristic feature of the amœba is its motility and on the warm stage it is constantly altering its contour. In the case of variola no definite pseudopodia have been seen. In glycerinated calf lymph the glycerine probably inhibits the movement of the parasite as well as that of the spores. M. Calmette,[1] in speaking of fresh calf lymph, remarks that these refractile grains, which he looks upon as the virulent element of vaccine, are mobile, but that in glycerinated vaccine pulp the granules are larger and immobile. The amœbæ found in human vaccine lymph fluid are exceedingly lively, numerous pseudopodia being continually extruded and retracted. All movements of these bodies cease at the temperature of the air, and to see them blood heat must be maintained. As I hope to publish shortly a paper on a method of cultivating the organisms of smallpox and vaccinia *in vitro*, a more detailed account of their life history is reserved for a future occasion.

Variolous matter contains a large number of amœbæ but

[1] 'Annales de l'Institut Pasteur,' No. 3, March 25th, 1901, p, 166.

relatively few extracellular spores. The amœbæ alter their contour on a warm stage, but there is no well-marked pseudopodium formation. The spores are motile when outside the parasites and are very refractile. There are also present large encysted parasites with a definite cell wall possessing a large nucleus with a definite nucleolus. The encysted parasite can be found in lymph which has been stored for a month or more. The amœbæ persist in variolous matter for many months. Absolutely fresh variolous matter can be fixed by immersion for fifteen minutes in equal parts of alcohol (spiritus rectificatus) and ether, and can then be stained with Loeffler's methylene blue; the parasite takes up the dye irregularly and *the nucleus not at all.* Suspended in a normal saline solution to which a trace of eosine has been added, the organism is found not to take up the dye. After fixing with a saturated aqueous solution of perchloride of mercury the spores can be stained with aniline gentian violet in thirty minutes but lose the dye on completing Gram's method.

Human vaccine lymph.—From the few opportunities afforded for examining this substance it cannot be stated at what date in the evolution of the disease the parasite makes its appearance, but it is conjectured that the height of the inflammatory process, the eighth or ninth day, is coincident with the presence of the maximum number of amœbæ. It has been stated before that the best day for collecting human vaccine lymph for the purpose of seeing the organism is the ninth day. It has been found that in lymph gathered on the tenth day the minute motile spores are very abundant, but either none at all or only a very few amœbæ are to be seen. On the eighth day of vaccination young parasites are to be found. This organism is very delicate and thus far success has not attended its fixation. The spore, which is exceedingly small, is actively motile for a few hours after its removal from the vaccine vesicle. It can be fixed with equal parts of alcohol and ether and stained with aniline gentian violet in half an hour. It is advisable to employ a $\frac{1}{18}$-inch objective to see these small elements and to use artificial light and carefully regulated illumination. The amœba as found in the vesicle of a vaccinated monkey seems to be a more hardy organism, since it can be found as late as the thirteenth day, is easily fixed with alcohol and ether, and stains well with methy-

lene blue; whether the nucleus stains or not has not been decided. The number of amœbæ present in such lymph is also much greater than is found in human vaccine. From the foregoing it will appear that human vaccine lymph differs from variolous matter and calf lymph in the relative paucity of amœbæ in the former compared with the latter, in the spontaneous disappearance of the amœbæ from human vaccine while these bodies persist for long periods in variolous and calf lymphs, and in the much smaller size of the human vaccine spore.

Glycerinated calf lymph, especially when fresh and virulent, contains an enormous number of spores and amœbæ of all sizes; both are for the most part immobile, the movement being probably inhibited by the presence of the glycerine, but under certain conditions both these elements show slow through distinct motion. The organism is comparatively hardy, persists for many months in capillary tube specimens, and contains large encysted forms, especially when a month or two old; in fact, the amœba shows a strong tendency to encapsulation. A nucleus cannot usually be made out in the fresh state, but if stained after fixing for a few moments with the fumes of a 2 per cent. solution of osmic acid, with aqueous safranin, or, still better, *in vivo* in a normal saline solution tinted with safranin, the nucleus shows up plainly, especially after 24 hours. From the irregular manner in which different amœbæ take up the dye the process can hardly be considered as a true staining one—*e. g.* a considerable number of the smaller forms do not stain at all, while the larger bodies are sometimes dyed quite deeply.

The following cytological method of staining calf lymph shows up the organism distinctly; the readiness with which any epithelial derivatives present in the lymph take up the brown colour throws the amœbæ into strong relief. A capillary tube of calf lymph is emptied of half its contents, then the tube is filled with a weak solution of Bismarck brown in salt solution, and the lymph and the solution are caused to mix in a centrifugal machine. In a few minutes the specimen will be ready and can be mounted as a hanging-drop preparation or more permanently in a shallow cell; this serves to avoid the pressure of the coverslip which would rupture the ectosarc of the amœba.

In varicella lymph I have also detected bodies similar in general characters to those of variola and vaccina. The proto-

zoon of this disease is present in the vesicular contents of the pock on the first day of the eruption and can also be found on the third day. Owing to the scantiness of the material at command nothing definite can be stated as to whether the parasite persists in stored lymph at the temperature of the air, as in variola, or whether it disappears spontaneously from the vesicular contents, like the protozoon of human vaccine lymph. The amœba is a spheroidal body about $\frac{1}{2500}$ of an inch in diameter, consisting of cytoplasm and a large, clear, circular nuclear body. The cytoplasm is finely granular and contains a number of coarser refractile granules, probably spores. This protozoon has one or two large nuclei, which, as in the similar organisms of variola and vaccinia, are only occasionally seen and that only when the organism is at rest. There are no nucleoli or vacuoles to be discerned. On the warm stage the organism assumes a variety of shapes. The nucleus if seen becomes lost; the protoplasm appears to swell up and to stream about in a very active manner. The spongioplasm and coarser granules become aggregated at certain spots, leaving spaces of clear hyaloplasm. The spores often show individual intra-cellular activity. The streaming protoplasm is extruded in all directions, either as blunt pseudopodia, but more often as greenish sharp thorn-like processes. If the temperature is reduced, the amœba may or may not return to its former resting shape, when it is for the most part circular in outline, with its granules evenly distributed in its substance, and any distinction between ectoplasm and endoplasm evinced on the warm stage is lost. The parasite can be fixed in a certain number of instances with equal parts of alcohol and ether. Only the very gentlest manipulation must be used in spreading the lymph, as the amœba is very easily destroyed. Fixed thus for 15 minutes and stained for ten minutes in Löffler's methylene blue, the nucleus or nuclei are found to stain very deeply, while the cytoplasm takes up the colour feebly. In this respect the organism differs materially from the amœba variolæ, in which, as already pointed out, the nucleus does not stain. It will be seen from this description how very unlike a leucocyte this body is; furthermore, in stained sections of the vesicle of varicella no leucocytes are to be found in the neighbourhood of the vesicle at this early stage. The organisms detailed in the foregoing descriptions are quite easy

of demonstration, and anyone following the directions given will have no difficulty in seeing them. From the above description of the parasites of variola and vaccinia it will be seen that they correspond closely with the organisms described by Funck under the name "sporidium vaccinale."[1]

For the assistance given to me in various ways I would like to tender my cordial thanks, in addition to those already mentioned, to D. H. W. Willson, Dr. John McFadyean, Dr. W. J. R. Simpson, Mr. A. Wynter Blyth, Dr. T. F. Ricketts, Dr. J. Massey of Graaff Reinet, Cape Colony, and to Dr. R. T. Hewlett, whose helpful suggestions and constructive criticism have been of the very greatest assistance to me.

November 15th, 1904.

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17. *Schistosoma cattoi: a new blood fluke of man.*[2]

By JOHN CATTO.

WHILE I was Resident Medical Officer at St. John's Island Quarantine Station, Singapore, cholera broke out on a passenger ship from China. Some four hundred coolies were quarantined. Amongst them was a Chinaman from the Province of Fukien who presumably had never been away from China before.

He died of cholera after three days' illness. He was plump for a coolie. During life it was found that the right lobe of his liver extended two fingers' breadth below the costal margin. The left lobe was a hand breadth below the sternum, and its percussion dulness merged into the splenic. The spleen was palpable 1 inch from the iliac crest, and its notch was in line with the anterior axillary fold.

A necropsy was made an hour and a half after death. The adipose tissue throughout the body was a prominent feature. The appearance of the peritoneum suggested repeated attacks of peritonitis. The appendices epiploicæ were thickened, and in some places matted together. The recto-vesical pouch was almost obliterated. Encasing the large intestine was a coat of fat, most marked at the mesenteric attachment. The mesenteric

[1] 'Brit. Med. Journ.,' February 23rd, 1901.

[2] The Craggs Prize Essay, 1904, London School of Tropical Medicine.

tissues were all thickened and loaded with fat. The mesenteric and prevertebral glands varied in size from a bean to a golf-ball, the largest forming a cluster near the duodenum. The liver was uniformly enlarged. Its surfaces were markedly nodular, its borders sharp and irregular, the whole presenting the appearance of a very coarse cirrhosis. Its consistence was greatly increased, but its colour was not appreciably altered. The coats of the gall-bladder were thickened, and a layer of fat almost completely encased this viscus, which was distended with clear mucoid, apple-jelly-like material containing several minute black gall-stones. The colon was much thickened throughout. The mucous membrane was swollen, hyperæmic, and friable, presenting numerous small circular, superficial erosions and patches of necrosis. The outer coats were very tough, almost cartilaginous, and showed no tendency to ulcerate. The rectum was three-quarters of an inch thick all round, and was adherent to the bladder. It nearly filled the true pelvis. Where adhesions had formed the bladder wall was thickened, but elsewhere it was healthy, and nowhere was the vesical mucosa diseased. The sigmoid was uniformly thickened; in tracing the bowel upwards the thickening became less marked and more patchy. The coats of the cæcum and appendix vermiformis were uniformly hypertrophied, the mucous membrane presenting small patches of ulceration and necrosis. The appendix was provided with a mesentery, and a distended lymphatic could be recognised running along its free surface. The liver and bowel cut gritty on section. The lower end of the ileum was thickened in patches, and the mucosa congested over corresponding areas. The enlarged spleen was pigmented. The stomach, pancreas, suprarenals, kidneys, heart, and lungs showed no signs of coarse disease.

As the lesions above mentioned were peculiar, some of the viscera were preserved. Sections of the liver, mesenteric lymphatic glands, and bowel were made in Singapore by Dr. Finlayson, and at the Kuala Lumpor Research Institute by Dr. Daniels. Numerous small oval bodies having a smooth, stout capsule were found. Opinions differed as to whether these were coccidia or the ova of some unknown parasite, but the case was published in the Journal of the Malaya Branch of the British Medical Association as a case of coccidiosis in man.

Subsequent examination in this country of sections of intestine showed ova and filariaform embryos in bundles in the mucosa and villi of the intestine. These, along with other specimens, were shown at the Medical Research Club, London, but no definite conclusion regarding the nature of the oval bodies was come to. An eminent German authority, to whom pieces of tissue were kindly sent by Dr. Bulloch, stated that "the oval bodies were neither coccidia nor the eggs of a trematode, but those of a nematode of unrecognisable species," etc. At Sir Patrick Manson's suggestion, to whom the specimens were shown, I devoted my whole time to working out the case at the London School of Tropical Medicine, where systematic examination and sections of all the preserved tissues were made. Soon after I commenced investigating, nematode embryos were found in smear preparations from the large intestine, and one was found in the vessel of a mesenteric lymphatic gland. These facts, coupled with the juxtaposition of ova—some empty—and embryos in the mucosa and villi of the intestine, led to the suggestion of a nematode infection, but as no evidence of a differentiated embryo could be seen in any of the eggs, even in those lying in close proximity to the bundles of free embryos, one hesitated to adopt this conclusion. Subsequently in sections of the mesocolon I found adult trematodes, male and female, in the blood-vessels, the ova in the uterus of the female corresponding in every particular with the oval bodies found in the various viscera. It was now clear that I had to deal with concomitant trematode and nematode infections; that the oval bodies were the ova of the trematode; and that their close association with filarial embryos was merely accidental.

A preliminary paper was read and drawings with specimens exhibited at the meeting of the British Medical Association at Oxford. Later, on continuing my dissections, entire mature worms were found in the smaller mesenteric blood-vessels. It was difficult to determine the nature of the vessels in which the mature parasites lay. They were manifestly blood-vessels, but whether arteries or veins was not so evident. I submitted my preparations to several eminent physiologists and pathologists. Unfortunately, there was no unanimity among them as to the arterial or venous nature of the vessels. I am constrained therefore to admit that this important point is for

the present unsettled. My own conviction, however, is that the parasites occur in both arteries and veins.

Parental Forms.

The male is 9 mm. long, less than half a millimetre broad, and, in my spirit preparations, of a light brown yellow colour. The measurements are only relative as they are taken from spirit specimens. Three entire adult males, with fragments of others, were found. They closely resemble those of schistosoma hæmatobium, having their lateral borders incurved ventrally, thereby forming a canal groove along the entire length—the gynæcophoric canal—in which the female lies. The anterior extremity is blunt, with a terminal sucker in which the mouth lies. The dorsal lip of the sucker is longer than the ventral. Behind the sucker the body is slightly constricted, forming a neck. The worm attains its maximum breadth at the posterior sucker, which lies ventrally in the gynæcophoric canal about half a millimetre behind the anterior sucker, whence the body tapers gradually to a truncated posterior extremity. The posterior sucker is oval and trumpet-shaped, its long diameter being transverse; it is larger and more muscular than the anterior. Both suckers are retractile.

The alimentary system consists of a mouth furnished with a sphincter, a strong muscular œsophagus, and two cæca joining posteriorly to form a terminal ampulla. The œsophagus, surrounded by small glands, is constricted at its middle, and divides, just anterior to the acetabulum on which rests the posterior sucker, into the two cæca which run along either side of the body. Three anastomoses of cæca were made out.

The excretory system ends in an excretory pore which is subterminal and ventral. The nervous system has not been satisfactorily determined. The reproductive system consists of a lobular testicle or testicles, vesiculi seminales, vas deferens, and genital pore with its sphincter, opening centrally into the gynæcophoric canal behind the posterior sucker.

A distinctive feature of this schistosome is the absence of ciliated warts on the integument, the presence of which constitutes so marked a feature of the African worm. Minor anatomical differences are: (*a*) smaller size of the worm; (*b*) its longer vas deferens; (*c*) the characters of the testes.

FIG. 37.

Male worm with a portion of female. A, Male worm, showing cæca. B, Female.

FIG. 38.

Male worm. Note smooth cuticle.

The female (Fig. 37, B) is almost cylindrical (diameter 0·113 mm.), longer, more slender, and darker than the male. The cervical constriction is quite as marked as in the male. The suckers, alimentary and excretory systems correspond with those of the male, except that the excretory pore is terminal. Owing to excessive fragility of the spirit specimen it was found impracticable to mount an entire specimen of the female worm.

The reproductive system consists of a muscular, central, elongated uterus occupying the anterior half of the body, and opening near the posterior sucker. The ova are arranged irregularly in single or in double rows. At the posterior extremity of the uterus are the shell glands and opening of the oviduct with the vitello-duct. Behind this the body bulges slightly, to taper subsequently to a sharply-pointed extremity. The bulging marks the position of the ovary; posteriorly are the vitellogene glands.

From the female schistosoma hæmatobium the following differences have been made out:

(*a*) The posterior sucker is larger than the anterior; the converse holds good in the schistosoma hæmatobium.

(*b*) The bulging in region of ovary is more marked.

(*c*) The arrangement of the yolk glands is different.

In both sexes minute, highly refractile spines are seen in the suckers and at their anterior extremities.

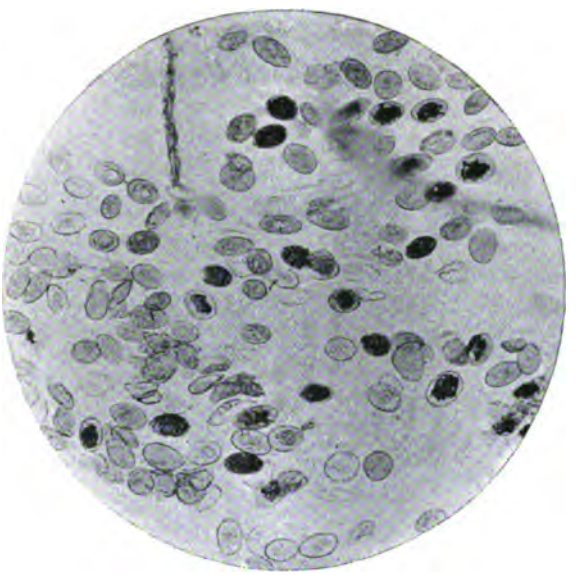
The eggs are yellow-brown in colour, oval, measuring on an average 70 μ long by 40 μ broad. They vary between 60 μ and 90 μ in length, and 30 μ to 50 μ in breadth. They have a stout, smooth shell on section. There is no trace of a spine or operculum. In the sections some of the ova were empty; others contained a central, circular mass which stained deeply; some contained cells staining at their periphery, whilst others had cells staining in the centre. These may or may not completely fill the ovum. In some cases the cellular contents were seen escaping from a ruptured ovum. In no one of the ova could distinct embryos be detected, although appearances suggestive of a developing embryo could be observed. The ova differ from those of schistosoma hæmatobium in their colour, shape, size, and in the absence of a spine. The bilharzia ovum is of a brown colour, contains a well-developed embryo, and is larger, 0·19 mm.

(Looss). Moreover, its ends are more pointed, and it is provided with a spine.

The ulcerative lesions of the bowel produced by the new species differ from the corresponding lesions of the bladder produced by S. hæmatobium in the entire absence from the former of the fungating masses so characteristic of the latter. Further, the new species does not give rise to the perihepatic nodules as described by Sandwith in bilharziosis.

In addition to the character of the ova and to the anatomical

FIG. 39.



Showing ova, as they appeared in a transverse section of the vermiform appendix, in the submucous tissue.

differences already noted, there are certain other points which serve to differentiate the species.

(1) The habitat of S. hæmatobium is reputed to be venous only, whereas the habitat of the new schistosome is mainly arterial; too much stress must not be laid on this point, seeing it has not been proved that the former cannot affect arteries or the latter veins.

(2) The ova of S. hæmatobium affect mainly the urinary system and escape from their human host by this channel. In the new species the ova apparently exclusively affect the

alimentary system, escaping by this route from their human host.

(3) In this case there is a much more general infection of abdominal viscera, for ova of S. hæmatobium have not been found in the pancreas and appendix.

(4) The geographical distribution differs, for no case of bilharziosis has yet been met with in China.

Histopathology.

The parent worms are found in small groups at the bifurcations of the smaller mesenteric vessels, and partially or completely plug the vessels. In one arteriole 0·621 mm. in diameter two complete sections of the male and female are seen *in copulâ*. Blood cells are occasionally seen between the wall of the vessel and the parasites.

Where ova accumulate they provoke at certain places a small-celled infiltration, which gives place later to a great proliferation of fibrous tissue. Pigment is seen in the liver and bowel. In the intestine from cæcum to anus the ova occupy roughly two concentric layers—the one subperitoneal, where the ova are comparatively scarce; the other in the submucous coat, where they are innumerable, in some cases densely packed. Between these zones in the muscular layers ova with their long axes at right angles to the bowel lie in single or in double rows. Ova are plentiful in the mucosa, are more numerous in the necrotic areas, and are seen apparently in process of extrusion at the margin of an ulcer.

Of the intestinal tract, the rectum and appendix are most affected; the distended lymphatic vessel in the appendix already referred to is choked with ova. Everywhere throughout the small intestine ova were found, but only in patches and in relatively small numbers.

The obliteration of the rectovesical pouch was probably caused by the irritation produced by ova accumulating in vast numbers in the wall of the rectum. In the many sections examined no ova were found in the vesical mucosa, though they were present in small numbers in the outer coats of the bladder.

In the liver the ova are plentiful, lying singly or in larger or smaller clumps embedded in the markedly hypertrophied fibrous connective tissue.

In many of the enlarged mesenteric lymphatic glands ova were found in the thickened trabeculæ.

In addition to the localities already mentioned ova were found in the outer wall of the gall-bladder, in the pancreas, liver capsule, fibrous coat of the larger mesenteric vessels, mesentery, pylorus, duodenum, jejunum, and ileum. Several sections were made of the round ligament of the liver and of the diaphragm without any ova being found.

Doubtless the life-history of the new schistosome corresponds with that of other trematodes, the geographical range of the intermediary host being the principal determining factor in its distribution.

That this case is unique is extremely improbable. When proper search has been made doubtless many additional cases will be found in the natives of the endemic districts. As a ready means of ascertaining the degree of prevalence and geographical range of the infection I would suggest systematic examination at *post-mortem* examinations of scrapings from the mucous membrane of the bowel, preferably of erosions or ulcerated patches. With a low power of the microscope only a few minutes are required to determine the presence or absence of the ova in such preparations.

The ova have probably been found many times in the course of ordinary microscopical examinations of fæces, but have been mistaken for the ova of ankylostoma duodenale, which they closely resemble.

It is interesting to note the accumulation of filariaform embryos in the villi, probably in the lacteals, of the intestinal tract, and their presence in fæces. I am not aware of any similar observation.

Diagnosis.

Sub Kingdom .	Vermes.
Class . . .	Plathelminthes.
Order . . .	Trematoda.
Family . .	Schistosomidæ.
Genus . . .	Schistosoma.
Species . .	Schistosoma Cattoi (Blanchard) 1904.

Measurements given below are from specimens found in hardened tissues:

	Female.	Male.
Length	?	9 mm.
Breadth	0·115 mm.	0·447 mm.
Breadth (near ovary)	0·134 mm.	—
Diameter at neck	0·041 mm.	0·180 mm.
Gynæcophoric canal	absent	entire length of body
Shape and size of posterior sucker	0·061 by 0·047 mm. (long. diam. longitudinal)	0·290 by 0·189 mm. (long. diam. transverse)
Shape and size of anterior sucker	0·051 mm. circular	0·124 mm. circular
Distance between centre of these	0·146 mm.	0·552 mm.
Genital pore	behind posterior sucker	behind posterior sucker
Excretory pore	terminal	subterminal
Tubercles and cilia	absent	absent
Spines in suckers	present but scarce	present

Habitat of adults: Mesenteric vessels.

Ova: Oval, with rounded ends and smooth, stout capsule destitute of spine and operculum.

Size: 0·065 to 0·090 mm. by 0·030 to 0·050 mm.

Found in intestinal tract and its appendages.

Number of cases: One.

Symptoms: Probably colic and dysentery.

Physical signs: Enlarged liver and spleen.

Geographical distribution: Province of Fukien, China.

Type specimen: Museum of London Tropical School of Medicine. Mounted in xylol balsam unstained from preserved formalin tissue.

It is possible that the filariaform embryos above referred to also escaped into the lumen of the bowels from the ulcers, for on making smear preparations from various parts of the bowel these embryos were found. In one smear thirteen embryos were present, but in many others none were found. These embryos had the following measurements and characters; these, however, cannot be taken as accurate, as none were got in fresh state.

Average length	0·300 mm.
Greatest thickness	0·008 „
Sheath	present.
Shape of head	truncate conical.
„ tail	sharp pointed.

(The sheath in many cases could not be seen, but embryos may discard it when in unnatural surroundings.)

Ova of trichocephalus dispar, anklyostoma duodenale, ascaris lumbricoides, in numbers, were found in the smears. Adult worms of all these were also found in the bowel.

I am deeply indebted to Sir Patrick Manson for much encouragement and criticism; and also for his sending specimens to the International Zoological Congress at Berne, where they were examined by Professor Blanchard, Drs. Loos, Ward, Stiles, Grassi, Monticelli, and other zoologists, who all agreed that the parasite was a schistosoma and new to science. Professor Blanchard has done me the honour of naming this new helminth *Schistosoma Cattoi*. To Drs. T. S. Kerr and E. E. Henderson the credit is due for the excellent drawings and photomicrographs.

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18. *On the relation of the suprarenal capsules to the sexual organs.*

By WILLIAM BULLOCH and JAMES H. SEQUEIRA.

IN recent years the observations and experiments of histologists and physiologists have thrown much light upon the nature and the functions of the suprarenal glands. It will, however, be admitted that these studies have not exhausted the problem of the *rôle* played by the glands in the animal economy. There are certain observations which go to show that there is some relationship between certain conditions of the suprarenal glands and the growth of the body, and it is with the object of throwing

some light upon this obscure condition that the following case is related.

On June 13th, 1901, a very stout girl, aged 11 years, was admitted into the North-Eastern Hospital for Children, under the care of Dr. Sequeira. She was suffering from pain in the præcordial region and dyspnœa on exertion. There was no history of previous illness, and her mother described her as having been thin and pale until fifteen months before, when menstruation began. Since then she had been observed to become very fat.

On admission the appearance of the child was remarkable. She looked like a stout little woman of about forty years of age. She was 4 feet 6 inches high, and weighed 6 stones 3 lbs. The face was large, and the expression heavy and dull. The complexion was that of a brunette, but with no abnormal pigmentation on the skin, which, however, was coarse and exhibited on the chin and lips a copious development of hair. Her breasts were large, resembling those of a sexually mature woman. The pubic region and the axillæ were covered with long hair. The abdomen, which was distended with fluid, showed in its lower part numerous atrophic striæ such as are met in pregnancy, and with rapidly growing tumours of this region. There was some cyanosis and considerable œdema of the abdominal wall and the legs. The upper parts of the thighs showed atrophic lines similar to those on the lower part of the abdomen.

The thyroid gland could not be felt on account of the quantity of fat in the neck, but there was no excess of fat in the supraclavicular regions.

The cardiac impulse was felt just outside the nipple line, and the area of dulness to percussion was increased. The first sound at the cardiac apex was booming, but there were no murmurs. The pulse rate was 90 per minute, and the tension was definitely raised.

Respirations were 50 a minute, movements of the chest were somewhat laboured, and moist râles were heard all over the lungs.

The abdominal cavity was distended with a large quantity of free fluid, and in the left hypochondriac region a tumour, evidently the spleen, was palpable. This extended for four fingers' breadth below the costal margin. It was dull on percussion, but no notch could be felt. Behind the spleen another mass could

be felt extending into and bulging the left loin. The actual shape of this second tumour, which appeared to be continuous with the spleen, could not be ascertained owing to the ascites. It was considered to be renal.

The liver projected a little below the costal margin. The quantity of urine passed in the first twenty-four hours was 44 oz. It contained albumen one fourth on boiling. There was no sugar, and the deposit was free from blood and casts. The patient had menstruated just before admission.

The bowels were freely opened by medicine, and this with the rest in bed brought about a rapid diminution in the œdema and ascites, and at the end of ten days the patient had lost nearly nine pounds in weight and was more comfortable. She was able to sit up in bed and amuse herself by reading and needlework.

On June 30th, however, signs of heart failure suddenly manifested themselves.

At 10 a.m. on July 1st the pulse rate was 144 per minute, the respirations being 22. The temperature, which had hitherto been normal, rose to 101° F., and in spite of stimulants and oxygen, the child gradually sank and died at 10 a.m. on July 2nd.

Autopsy.—The subcutaneous fat was found to be over one inch in thickness over the thorax, and half an inch over the abdomen. The labia and lower abdominal wall were œdematous, as were also the lower extremities. On opening the abdomen a large quantity of clear serum escaped, and the left hypochondriac and lumbar regions were found to be occupied by an enormous mass which had pushed the spleen forwards and the kidney downwards. The tail of the pancreas lay in front of the tumour and was not involved in it. When removed the mass weighed 3 lbs. 1 oz., and was found to be connected with the left suprarenal body, no actual part of which could, however, be recognised in the growth.

The tumour was of a rounded oval form. The consistence varied, but in some places it was almost diffluent. The cut surface presented an extraordinary diversity of appearance. Its general colour was a deep red, but scattered throughout it were irregular foci varying from a pin-head to the size of a tangerine orange, and of a colour varying from deep yellow to yellowish and even white. A considerable quantity of blood escaped when fresh cuts were made into the growth.

The right suprarenal body was, if anything, slightly enlarged. The spleen weighed 5½ oz.; it was lobulated, and did not contain nodules of growth.

The left kidney weighed 9 oz.; it was uniformly pale and somewhat tough. The tumour was easily stripped from it, and at no place could any evidence of secondary growth be found. The right kidney weighed 8 oz., and was also free from metastases. The liver weighed 4 lbs. 3½ oz. On section a small secondary nodule was found in the right lobe, and attached to its posterior border close to the gastric impression there was a mass the size of a hen's egg of similar appearance and consistence to that in the left suprarenal body. It was actually in contact with the latter, and may be considered as an extension of the primary growth. The heart weighed 11 oz., the right ventricle and auricle being distended with *ante-mortem* clot. The wall of the left ventricle was slightly hypertrophied. The thyroid glands and glandulæ parathyroideæ were the seat of considerable hypertrophy. Both lungs were thickly studded with secondary deposits varying in size from a pea to a walnut. The growths were sharply circumscribed, rounded and of reddish colour. In some hæmorrhages had occurred. The uterus was much larger than normal, the cervix and the body being of equal length, which indicated a much greater hypertrophy in the cervix than in the corpus. The ovaries were equal in size, and perhaps a little larger than normal. On section several corpora lutea were found, one being of recent date.

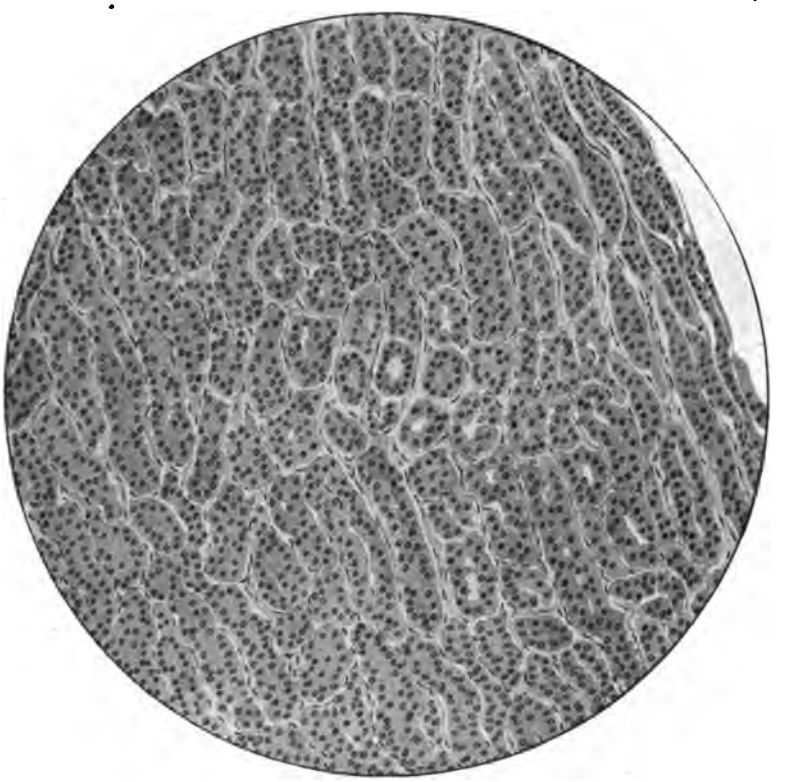
Parts of the primary growth and of the nodules in the liver and lungs were fixed in formalin and in corrosive sublimate, and, after embedding, sections were cut and stained with hæmatoxylin and suitable counterstains in the usual way.

Primary tumour.—With a low power the tumour presented a varied appearance at different parts, especially where secondary regressive changes had set in, and ended with necrosis and caseation. In the most recent parts of the tumour the structure is seen to be of a carcinomatous type. The analogy with the zona fascicularis and of the suprarenal body was so striking that this may actually serve for a description of the tumour features (see Fig. 40). Between the columns of cells were capillaries with endothelial lining. In some parts these capillaries were widely distended with blood so as to form sinus-like dilatations round the walls

of which sat the cells of the opened-out columns in several layers. With high powers the cells were more or less polygonal with rounded edges. Brown pigment granules could be seen here and there. The nuclei were round or oval and mostly rich in chromatin. Cells with chromaffinic characters were not observed.

Metastasis.—The nodules in the liver presented the same

FIG. 40.



A section of the growth described in the text. It consists of columns of cells closely resembling those of the adrenal cortex.

variegated appearance and structure as the primary tumour. The metastatic foci in the lung were sharply circumscribed and highly vascular, the vessels in many places being distended and separated from each other by the masses of polygonal epithelial-like cells. Commencing necrosis had occurred in several of the larger masses.

Taken as a whole, the tumour presented the characters of a carcinoma. In regard to the histogenesis, there is no doubt that

it originated in the left suprarenal body, and the marked resemblance to suprarenal cortex leads to the conclusion that the cells were really suprarenal cells. In other words, the tumour was a malignant hypernephroma, although the highly reticulated condition of the protoplasm which is so marked a feature in many hypernephromata was not apparent.

The brief points of interest in this case then were, that a girl of 11 who up to the age of 10 had been normal, showed precocious development as manifest in her size and bulk, the onset of menstruation, the development of hair on the pubis and face, and the maturity of the mammary glands. At the same time a tumour developed in the abdomen. After death the tumour was found to have arisen in the left suprarenal gland, and to be composed of adrenal tissue.

It might be supposed that the simultaneous occurrence of a suprarenal tumour with precocity was a matter of chance, but the study of the literature reveals a number of cases which seem to show that there is between these two factors the relation of cause and effect.

Colcott Fox (1) (1885) has recorded an interesting case of precocity in a girl aged 2 years. Normal at birth, she is described as having been "enormous" at the age of 10 months. When seen at the age of 2 years she was somewhat rickety, gross, and bloated, with a dusky pallor, but no pigmentation.

The surface of the body was quite remarkably hairy, especially about the genital and paragenital regions. The appetite was ravenous, but the intellect was dull. A large swelling was detected in the abdomen, but the patient died before it could be removed.

The autopsy showed the vulva, labia, and clitoris, to be the seat of precocious development. A large tumour apparently connected with the kidney and occupying the posterior and left aspect of the abdomen was found. No right suprarenal gland could be detected. The tumour weighed 1½ lbs., and occupied site of left suprarenal body. The lungs contained several nodules of new growth which, like the primary abdominal growth, turned out to be a large-celled sarcoma. The vena cava inferior was enormously distended and hard, and on opening it, a decolorised clot was found adherent to the wall, and extending up into the right auricle and through the auriculo-ventricular orifice into the right ventricle.

Fox in his paper also refers to a specimen in the museum of St. George's Hospital, which was obtained by Dr. Dickinson. It is a large spherical, somewhat lobulated tumour of the suprarenal capsule of a child aged 3 years. She was intellectually dull, had a harsh voice, a gipsy colour without actual bronzing, and is stated to have had an enormous appetite. She presented a remarkable development of hair dating from the first year.

J. Ogle (2) long ago (1864) described a peculiar case in the person of a little girl aged 3 years. She was "unusually stout," weighed 44 lbs., and measured 2 feet 10½ inches in height; circumference of abdomen 2 feet 3 inches. She had a peculiar sullen look, and there was a large amount of hair over the whole of the body. The eyebrows were excessively thick and bushy, and a decided moustache existed on the upper lip. There was a large amount of curly hair on the genital organs, which were well developed. Everywhere the skin was of a gipsy coppery colour, but not bronzed.

One month after being first seen by Dr. Ogle she was admitted into the hospital, but died the following day. *Post mortem* all the organs were normal with the exception of left suprarenal capsule, which was the seat of a "large encephaloid cancerous growth, weighing 2 lbs. 2 oz." (This case is also described by Pitman, 'Lancet,' 1865, Part I, p. 175.)

Linser (3) has described the case of a boy aged 5 years and 7 months. On admission to the hospital he was found to measure 138 cm. in height, and was supposed to be about 16 or 18 years of age. With the exception of the last four molars all the teeth had erupted. The mons veneris was covered with hair and the penis was 8 to 9 cm. long (*in statu erectionis* 12 to 14 cm.). The testicles were as large as pigeons' eggs. A long series of measurements made in comparison with a 142 cm. long normal boy, aged 15 years, showed that the patient exceeded most of the normal measurements.

For a year the patient had complained of pain in the side. The clinical diagnosis was a new-growth of left kidney. Exploration was made, and an inoperable tumour as large as a man's head was encountered in the region and attached to the left suprarenal body.

After death a malignant tumour of left suprarenal was found, with rupture into the vena cava. The lungs contained many meta-

stases. The thymus was not found. The thyroid and pineal glands and the hypophysis were normal in size. The suprarenal tumour was largely necrosed and in part calcified. The tumour-cells were polygonal in shape, with a rounded or oval nucleus. Glycogen was not found, but in general the cells were so like those of the zona fasciculata of the suprarenal body that a diagnosis of hypernephroma was made.

Orth (4) reported the case of a girl, aged 4½ years. For nine months before admission into the hospital she had pubic hair, and during the last six months of life a beard so strong that it had to be shaved. The external genitals were the seat of precocious development, the clitoris being like a small penis. From her second year a tumour had been noticed in the region of the right kidney. The necropsy showed the tumour to have arisen in the suprarenal body and to have formed secondary metastases in the lungs and liver.

The tumour was composed of polygonal cells of varying size, some showing a giant nucleus; others had several nuclei. Orth held the tumour to be a carcinoma, although he points out that the analogy with suprarenal tissue was unequivocal.

Dobbertin (5) mentions the case of a girl, aged 14 months, who, according to the story of the parents, was born with a tumour in her abdomen. At the time of admission into the hospital this tumour was the size of a fist. It was situated at the upper pole of the left kidney, which was removed along with the tumour, but the patient died.

The *post-mortem* protocoll (Stroebe) notes the presence of fairly thick, long, brown hair (5 cm.) on both great labia. On lower part of abdomen and lateral aspects of thorax, the back, and cheeks, there was also a considerable development of hair. The tumour was of suprarenal structure.

Linser also refers to several other cases, but with the exception of the last of them, I have not been able to verify the references he gives. He quotes Tilesius (1803) as having observed in a girl, aged 4 years, who measured 80 cm., an enormous formation of adipose tissue, with premature development of the mammæ and the pubic hair. The autopsy revealed a tumour the size of a goose's egg in the site of the left suprarenal capsule with metastases in the liver.

He also refers to a case published by William Cooke in the

'Philosophical Transactions' for 1756. The patient, a girl aged 7 years, was enormously fat and had a copious growth of hair on the face and genitals. There was a large tumour in the site of the left suprarenal body.

Bevern and Romkild ('Neues Journal d. prakt. Heilkunde,' 1802) reported the case of a girl, aged 3½ years, who looked like a woman of 20. She was very fat, had abundant hair on her genitals, also on her face. The necropsy showed a large tumour connected below with the uterus, but above with a large glandular body in the region of the left curvature of the colon and the spleen.

Linser refers lastly to a specimen in the Museum of the Royal College of Surgeons. In the College catalogue this is described as follows, No. 3518 E: "A large solid tumour which has replaced the right adrenal body. It measures five inches in length and from three to five inches in its other diameters. The anterior surface is convex, where it is partly covered with peritoneum, and posteriorly it is flattened. At the upper right-hand corner a portion of the inferior cava is adherent to the tumour, and a polypoid mass of growth protrudes into its lumen from the mouth of the adrenal vein. On section a tough capsule is seen enclosing a spongy tissue, but none of the normal adrenal body can be discerned. Histologically the growth is a soft carcinoma, composed of elongated alveoli filled with large granular epithelial cells. The alveoli are separated by capillary vessels and a very scanty stroma. From a single woman, aged 32 years, who was admitted to an asylum for mania and epileptic fits. She was very anæmic, menstruation was absent, and her face and extremities were so thickly covered with hair that a razor had to be used. Death occurred three months after admission. At the autopsy secondary growths were found in the liver and neighbouring lymphatic glands."

Dr. Ritchie, of Oxford, has communicated to me an account of a case which came under his notice some years ago. It was that of a girl, aged 4 years. An osteotomy operation was performed upon her for some deformity, but she died three days later without any apparent cause except that the wound had become slightly infected. The autopsy showed that with the exception of one suprarenal gland the viscera were healthy. The gland in question was the size of a kidney and was the seat of a tumour.

The condition of the sexual organs of this child had been the subject of remark during life. At first they were thought to be hermaphroditic in character, but the examination made by Professor Arthur Thomson showed them to be normal except that they were in size the organs of a developing woman. There was no history of menstruation, but there existed an abundant development of pubic hair.

Through the kindness of Dr. Ritchie I have had the opportunity of examining the sections of the suprarenal tumour. There exists a considerable difference from our case; with a low power an immense number of very large cells can be seen, mostly with several nuclei; with a high power, the cells are separated from each other by a fibrillary and granular ground substance. The cells are definitely polygonal and the nuclei are deeply stained. Apart from the giant cells there are large numbers of small cells, mostly with a single nucleus. The histogenesis of the growth is difficult to make out, although its type is that of a sarcoma.

C. E. Adams has, in the communication following the present, recorded a case of similar character. The patient, a boy, aged 14 years, was normal until the age of 10, when puberty set in. There was marked development of the beard and great muscular development. The face was dusky but not bronzed. A large tumour was discovered in the abdomen which on exploratory operation was found to be inoperable. The patient succumbed seventeen months later. The autopsy showed a huge tumour in the site of the left suprarenal gland and extending into the liver. The microscopic examination of the primary growth showed it to be a malignant hypernephroma taking its origin in the adrenal cortex.

A tabular analysis of these eleven cases is given below, from which it will be seen that with the exception of two cases, viz. our case (11 years) and Adams' (14 years), all the others have been observed before the age of 7. In Dobbertin's case the suprarenal tumour appears to have been congenital. Only two cases, Linser's and Adams's, occurred in the person of boys. In the females there was not only a premature development of hair on the pubis and in the axillæ associated with precocious development of the sexual organs, but most observers also noted a remarkable hirsuties of the whole body or of the face. No true bronzing,

such as is met with in Addison's disease, is recorded, although an increased pigmentation is noted several times. With the exception of the cases of Ritchie and Colcott Fox the tumour where examined appears as a carcinoma or hypernephroma.

No.	Observer.	Age of patient.	Sex.	Clinical manifestations of precocious development.	Nature of suprarenal tumour.
1	Bulloch and Sequeira	11	F.	Hair on chin and upper lip, pubis, axillæ, fully developed mammæ, menstruation	Hypernephroma malignum.
2	Colcott-Fox	2	F.	Pubic hair	Large-cell sarcoma.
3	Dickinson	3	F.	Pubic hair, harsh voice	?
4	J. Ogle	3	F.	Hair all over body, moustache, pubic hair	"Encephaloid cancer."
5	Linser	5	M.	Pubic hair, precocious development of genital organs, great growth of whole body	Hypernephroma malignum.
6	Orth	4½	F.	Beard, precocious development of external genitals	Carcinoma (hypernephroma ?)
7	Dobbertin	1 year 2 mos.	F.	Hair on genitals	Hypernephroma.
8	Tilesius	4	F.	Pubic hair, premature development of mammæ	?
9	Wm. Cooke	7	F.	Obesity, facial and pubic hair	?
10	Bevern and Romkild	3½	F.	Obesity, pubic hair, facial hair	?
11	Ritchie	4	F.	Premature development of sexual organs	Sarcoma with large cells.
12	Adams	14	M.	Facial hair, notable muscular development	Carcinoma.

As a further support to the view that there is some connection between the development of the sexual organs and the condition of the suprarenal bodies are the cases of precocious development where the gland has been simply hypertrophied.

Marchand (6) has described in detail the case of Elizabeth Wilhelm Moll, who, baptised as a girl, was, as the result of a medico-legal examination at puberty, declared to be a male. In the hospital before her death, at 50 years of age, she was regarded as a man. *Post mortem* showed the case to be one of hermaphroditismus spurius femininus. There was a large penis-like clitoris, well marked scrotum, fairly large prostate. The vagina opened into the colliculus seminalis and presented at its orifice a trace of a hymen. The uterus was fairly well formed, but ovaries were quite atrophic. The ostiæ of the tubes were closed. The body in general presented male characteristics. The

mammæ and nipples were small. There was a strong growth of hair on the face, which had been shaved. The remarkable thing was a colossal hypertrophy of the suprarenal bodies, the left of which measured $8\frac{1}{2} \times 6 \times 3$ cm. and the right $7\frac{1}{2} \times 6 \times 2$ cm. There was also a large accessory suprarenal measuring $5 \times 3 \times 3\frac{1}{2}$ cm. The normal measurements of the gland as given by Quain—30–60 mm. from above downwards, about 30 mm. from side to side, their thickness being 4–6 mm.

Crecchio (7) describes a peculiar case of hermaphroditism where the individual, baptised as a girl, was afterwards brought up as a boy, and as a man contracted gonorrhœa twice. Death took place at the age of 40. The physiognomy was that of a male. The breasts and nipples were small, the chest was hairy. Penis 6 cm. long; *in statu erectionis*, 10 cm.; scrotum absent.

At the autopsy, the uterus, tubes, ligamenta lata, and ovaries were found, and with the exception of the last (which were small) they were normal. No corpora lutea were seen. The suprarenals were the seat of extensive hypertrophy.

Otto (8) (1816) has also recorded a case of hypertrophy of the genital organs associated with hypertrophy of the adrenals.

References to a probable relationship between the suprarenals and the sexual organs are also to be found in the older literature. It was particularly developed by Friedrich Meckel (9) (1806) from his studies in teratology and comparative anatomy. In an acardiac monster he noticed that the sexual organs and adrenals were absent. He also stated his belief that animals gifted with prepotent sexual powers had large suprarenals. Akin to man and the monkey in this respect he placed the guinea-pig. In birds and amphibians he found that the suprarenals increase during the period of heat. In these views he was supported by Huschke (10), but opposed by Rayer (11), Nagel (12), and others.

Hutchison (13) has recently described an interesting case of hemihypertrophy with enormous increase in the size of the suprarenal body on the same side. The patient, a child, aged 4 months, was brought to the London Hospital presenting a remarkable unilateral hypertrophy affecting especially the arm and leg, and to a certain extent the trunk on the left side. The hypertrophy was of the "false" variety, as it apparently did not affect the bones. Shortly after being seen the child contracted and suc-

cumbed to a broncho-pneumonia. The autopsy showed the enlargement to be due to increased deposit of fat in the connective tissue. The bones were symmetrical; the brain, pineal and pituitary glands were normal. Most of the paired organs were larger on the left side than on the right. Left kidneys 56 grammes; right, 28 grammes. Left suprarenal 42 grammes; right, 14 grammes. Left testicle, 2·3 grammes; right, 0·55 grammes. The condition of the enlarged suprarenal appears to be a hypertrophy and hyperplasia.

I have been unable, however, to find any other cases (see Lewin, 14) showing such changes in one suprarenal and associated with hemihypertrophy.

The opposite condition, viz. a retarded development of sexual characters in association with a hypoplastic or atrophic condition of the adrenals, is also met with.

Wiesel (15), reports the case of a girl, aged 18 years, in whom it was observed that there were no axillary hairs, and but one or two on the mons veneris. The mammæ were practically non-existent, the nipple being rudimentary. The genital organs were in the infantile state. The autopsy disclosed a striking hypoplasia of the adrenals.

Karakascheff (16) refers to two cases of atrophy of the adrenals. In one, a female, aged 39 years, who had borne two children, the menses ceased at the age of 27. At the autopsy it was noted that the mons veneris, labia, and axillæ were practically hairless. The uterus, ovaries, and tubes were small, the parenchyma of the ovary being very atrophic. Both suprarenals were so entirely atrophied that it was difficult to distinguish them from the surrounding fat.

In another case running an acute course in a male, aged 41, years, it is noted that the testicles were small. The suprarenals were completely atrophied.

In one of the interesting cases of progeria or premature senility described by Hastings Gilford (17), it was noted *post mortem* that there was a "shrivelled" condition of the suprarenal bodies.

Zander (18) also observed in a fairly large number of monsters in whom the suprarenals were defective that the genital organs were imperfectly or incompletely developed in association with defects in the cerebrum.

It is known that precocious development with macrosomia may occur without lesions of the suprarenal body.

C. Ogle (19), *e.g.*, has recorded the case of a boy, aged 6 years, who showed a marked premature development of the penis and the pubic hair. After death a tumour was found involving the pineal gland, the tumour apparently being an alveolar sarcoma with hæmorrhages and cysts.

Heubner (20) has observed a similar case of pineal tumour in a boy aged 4½ years, with abnormally large penis, scrotum and testis, and abundant pubic hair.

Fritsche and Klebs (21) have attempted to refer excessive growth of the body to tumour conditions of the thymus gland.

And lastly, the condition of acromegaly is usually, although not necessarily—see literature in Sternberg (22), Cagnetto (23)—associated with pituitary blastomata.

Further, cases are recorded of blastomata in the suprarenal bodies of young children in whom no evidences of precocious development were manifest. Thus Greenhow (24) observed a tumour in one suprarenal body of a girl aged 12 years, and although described by him as a carcinoma, Hulke and Dickinson reported upon it as a sarcoma. In the majority of cases of primary suprarenal tumours occurring in infants and unassociated with precocious development, the neoplasms have been for the most part sarcomata and especially lymphosarcoma. In this category come the cases reported by de Ruyter (25), M. Cohn (26), Lazarus (27), Amberg (28), Pepper (29), Brüchanow (30), Reimann (31), Orr (32), Earle and Weaver (33), Gade (34), Mankiewicz (35), Rupprecht (36).

Primary malignant disease of the suprarenal glands in adults has been frequently observed, but throws no light upon the present question. Excellent analyses of the literature will be found in the papers of Rolleston and Marks (37), and Woolley and Adami (38).

In support of the view that the suprarenal capsules are in some way connected with the growth of the body, reference may further be made to the well-known fact that defects in the development of the cerebrum, especially the condition of anencephaly, is in a large percentage of cases associated with aplasia or hypoplasia of the adrenals. This discovery, generally accredited to Hewson, appears really to have been made by Morgagni. In recent years it has been exhaustively treated by Zander (*l. c.*)

Summary of cases of primary tumours in the suprarenal in children without signs of premature development.

Observer.	Sex.	Age.	Nature of tumour.
Lazarus	?	4 years	Sarcoma.
Cohn	Female	9 months	Sarcoma medullare (diagnosis by Virchow).
de Ruyter	Male	10 days	Lymphosarcoma (diagnosis by O. Israel).
Amberg	Female	2 months	Sarcoma probably from medulla.
Pepper	Female	5 weeks	Lymphosarcoma.
Brüchanow	Female	14 months	Carcinomatous type.
Reimann	Female	6 months	Melanotic carcinoma (both glands).
Orr	Female	7 weeks	Sarcoma of liver and supra-renal primary ?.
Earle and Weaver	Male	3 years	Sarcoma.
Gade	Male	4 years	Sarcoma.
Gade	Male	6 years	Sarcoma.
Mankiewicz	Female	2 years	Sarcoma.
Rupprecht	Female	2½ years	Adenoma of supra-renal.

In the cases of Rupprecht and Brüchanow there is no clinical history.

and Alexander (32). Zander came to the conclusion that the proper development of the adrenals can only go on when the brain is intact. The standpoint taken by Alexander is, however, the reverse of this, viz. that the adrenal aplasia is primary, while the cerebral defect is secondary, a view which, however, has been adversely criticised by Lubarsch (33).

There are likewise other facts which point to the view that in some way or other the adrenal gland discharges its most important functions during the growth of the body. It has long been known that at the end of the third month of fœtal life the adrenals are actually larger than the kidneys. By the time of birth, however, the kidney has gained an advantage, being about three times as large as the adrenal, while in adult life the proportion is about 44—1 (Rolleston). The question as to the amount of growth which the suprarenal undergoes after birth does not appear to be definitely settled. Rolleston (*l. c.*) says that "after birth the suprarenal capsule continues to increase in size, and, like other organs, attains a size roughly corresponding to the whole body. On the other hand, Quain (9th edition) states that the glands are nearly as large at birth as in adult life. In favour of the view that the suprarenals do not go on

actively growing may be mentioned the poor successes which have followed attempts to transplant the suprarenals even in animals of the same species—Schmieden (42), Poll (43). The most favourable of the few positive results claimed by Poll were in the case of young animals. On the other hand, the extirpation of one gland in very young animals leads to hypertrophy of the remaining gland. Where the operation is undertaken in older animals, hypertrophy is not seen—Stilling (44), Vellich (45), Simmonds (46, 47), Wiesel (48), Charrin and Langlois (49).

An important support for the view we have suggested would be expected from the study of the embryological development of the suprarenal gland, but here, again, in spite of a considerable amount of study, unanimity has not been reached. We know that the suprarenal glands are of ancient origin, as, with the exception of the Dipnoi and Cyclostomata, they occur in all Vertebrates. We also know from many experiments that they are vital organs. Even in amphibians they cannot be destroyed with impunity (Abelous and Langlois, 50, 51). It is also known with certainty that the so-called suprarenal glands of the higher vertebrates are compound structures containing two widely differing elements, the medulla corresponding to the paired suprarenals of elasmobranchs while the cortex is the homologue of the interrenal body—Balfour (52), Kölliker (53), Swale Vincent (54), A. Kohn (55), Aichel (56). There is also no doubt but the medulla is developed from cells that separate off from the sympathetic ganglia. Physiologists are also agreed that the functions of the suprarenal hitherto discovered are to be identified with the medulla only. The important question then is, what is the origin and function of the cortex which, as we have seen, is an independent body in the elasmobranchs? One can recognise the cortical *anlage* as a group of cells close to the anterior end of the genital gland. Two views have been suggested as to the origin of these cells. The first is that they arise by proliferation of cells at the inner ends of the invaginations of the cœlomic epithelium at the anterior end of the Wolffian ridge and just lateral to the genital gland; the other view, held by Janossik and Mihalkovics, that they come from the germinal epithelium at the anterior end of the genital ridge. In either case it is quite conceivable that cells which normally go to the genital gland might become involved in the suprarenal cortex.

That there is a possible connection of the suprarenal glands with the sexual system is seen even as low as the frog, where there are seasonal variations in the structure of the gland corresponding to the period of pairing. Apart from the "cortical" cells and the medullary (chromaffinic) cells of the suprarenal of the "winter" frog, Stilling (57) has shown that in summer considerable changes occur consisting of a disappearance of the medullary tissue and the development of remarkable cells which from the time of their appearance are called "summer" cells. This is coincident with the pairing of the frogs. Gottschau (58) has also shown in the case of rabbits that the suprarenal capsules undergo changes in volume during pregnancy, the outer zone of the cortex becoming twice the normal thickness at the expense of the medulla and inner zone.

Conclusions.—(1) There exists in medical literature the reports of a series of cases where in quite young children there has been a precocious development of hair on the face and on the genital regions. There has usually been a premature development of the genital organs and the accessory genital glands at the same time.

(2) The pathological findings have been either carcinomata (hypernephromata) or hypertrophy of the suprarenal capsules. Atrophy and hypoplasia of the suprarenal glands may be associated with disappearance or non-development of hair on the pubis and a hypoplasia of the genital organs.

(3) Cases of primary blastomata of the suprarenal glands and unassociated with precocity are usually lympho-sarcomata.

(4) The cortex of the suprarenal gland is probably connected in some way with the growth of the body and the development of puberty and sexual maturity.

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February 7th, 1905.

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19. *A case of precocious development associated with a tumour of the left suprarenal body.*

By Chas. E. Adams.

R. W. T., male, aged 14 years 9 months, first presented himself for examination on July 31st, 1902, and complained of a "lump" in the abdomen. There was no pain, and his general health was excellent. Examination revealed the presence of a regular hemispherical swelling four inches in diameter, its centre touching the abdominal wall at a point four inches to the left and two inches above the level of the umbilicus. The swelling was capable of displacement only to a very slight degree.

Considering his age the boy presented remarkable appearances of precocious development. As a child nothing unusual had been observed about it, but puberty set in at the age of 10 years, from which time, although he increased little in height, he developed great muscular strength, excelled in athletic sports, and defeated all competitors. For two years his complexion had been observed to be plethoric and dusky, and during this period the growth of hair on his face had to be shaved almost daily. His general appearance was that of a sturdy little man.

On September 20th, with a view to diagnosis and possible removal of the tumour, an exploratory operation was performed and a large inoperable mass was encountered in the region of the left kidney. The tumour was solid and its surface was covered

with greatly dilated veins. It was regarded as a retroperitoneal sarcoma. Immediately after the operation the tumour increased with great rapidity, but later at a slower pace again. In spite of the size of the tumour the patient suffered relatively little inconvenience. In September, 1903, *i. e.* one year after the exploratory operation, the liver was found to be extensively enlarged, its edge projecting about four inches below the costal margin.

During October, 1903, the fæces became pale and the urine showed bile pigment. By this time the tumour practically filled the left half of the abdominal cavity, and the abdominal wall showed enormous atrophic striæ.

On January 7th, 1904, he was taken suddenly ill with acute lumbar pain. The fæces had become almost colourless, and the tumour had extended about 2 inches beyond the middle line of the abdomen into the right side. The abdominal circumference measured 39½ inches. From this time onwards he rapidly lost weight and died suddenly on January 30th, seventeen months after the exploratory operation.

Autopsy.—Permission was given for a partial autopsy, which was performed on February 1st. On opening the abdomen the stomach and intestines were found to be normal. The spleen was not enlarged, but showed a few small yellow spots at the middle of its anterior edge. The liver, which was enormously enlarged, weighed 15¼ lbs., and was thoroughly infiltrated with numerous yellow masses of all sizes up to a walnut. On incision these masses were found to be of cheesy consistence and appearance. The tumour mass weighed 8½ lbs. and was covered by a capsule consisting of thickened peritoneum. On section the tumour presented a variegated appearance, in parts resembling the cheesy masses in the liver, at other places being of firmer consistence and even gritty. It was firmly adherent to the left kidney, which, however, was not involved. No trace of the left adrenal gland could be found. The right was normal. Pieces of the liver, the tumour, and the spleen were hardened, cut, and stained in the usual way, their histological characters, reported by Dr. J. C. G. Ledingham, being as follows:

For histological examinations, only four sections were at my disposal, viz. one each of the liver, spleen, kidney, and primary growth.

Unfortunately, owing in all likelihood to delay in fixation of

the tissues, the specimens were not so well adapted for accurate microscopical examination as one might have desired.

Primary tumour.—With a low magnification, the tumour appears to be roughly divided by a broad band of dense connective tissue into two unequal parts which present quite distinct appearances in the arrangement of their cellular elements.

The smaller portion consists of interlacing columns of cells separated by dilated capillary channels and a fine connective-tissue supporting framework. In some parts, however, the thin-walled blood-channels have increased so enormously in size and number as either to obliterate entirely the cell strands or produce a more or less complete disintegration of them into individual cell elements. Along with this angiomatous condition has gone a marked development of perivascular connective tissue which has further contributed towards the dissolution of the columns.

The cells belonging to the columns are of fairly large size and polygonal shape. They possess an abundant cytoplasm which invariably shows vacuolation due to fat. The nucleus is small and situated for the most part excentrically. Here and there one can recognise between two adjacent groups of cells a small lumen which frequently contains a yellowish-green mass of pigment. On the whole, apart from the fibroses and the angiomatous condition, this part of the tumour presents an appearance exactly similar to that of the zona reticularis of the suprarenal cortex, and in all probability represents the remains of that structure.

The major portion separated from the smaller by the above-mentioned band of connective tissue is far more homogeneous in structure, and almost entirely cellular. In spite of the shrinkage that has taken place during the process of fixation, it can be seen that there is a general arrangement into short columns and more or less circular groups separated from each other by intervening capillary channels, the endothelial lining of which forms a sort of basement membrane for the support of the tumour-cells. The endothelial cells of the capillary are still visible. The individual tumour-cells moreover are demarcated from each other by a fine granular membrane, which is evidently produced by the protoplasmic processes of the cells themselves.

The uniformity in type of the cell elements is remarkable in spite of the variation in size. They are nearly all of polyhedral

shape, with abundant vacuolated protoplasm and excentrically placed nuclei. The possession of cell processes is also notable.

In size they vary from 8 μ to 30 μ, and fairly numerous mononuclear and polynuclear giant forms are observed. A few dividing forms were also noted. No true nucleolus was recognisable in the tumour-cells.

There is practically no development of cirrhotic tissue, but thin-walled vessels are of frequent occurrence.

Liver.—Owing to the enormous infiltration with tumour element it is somewhat difficult to pick out the still intact liver acini, and more so as the tumour-cells present a great similarity to true liver-cells. In the subcapsular region, however, and in the neighbourhood of the portal areas one can still distinguish a few partially intact liver-columns. Practically the whole of the liver substance is replaced by tumour-cells, which present no definite arrangement into columns or groups. They are of the same polyhedral contour as those met with in the primary growth, but distinctly smaller in size. Though most of them lie promiscuously in what were once the interacinous capillaries, we note numerous interlacing columns of these cells placed end to end in tesselated fashion, recalling exactly the distribution of the cells of the zona reticularis of the adrenal cortex. Numerous small masses of bile pigment lie among the tumour-cells.

Kidney.—A very marked increase of the renal connective tissue is noted. The glomeruli are numerous and of large size, the capillaries of the tuft being much dilated and containing an excess of endothelial cells. In the great majority of the tubules the epithelial cells are swollen and granular, and their nuclei stain indifferently. There is no evidence of metastatic tumour masses in the kidney.

Spleen.—The section has been made through the yellow masses noted in the protocol. These were found to be small, ramifying, subcapsular cysts, containing granular *débris*, with more or less intact polyhedral cells like those of the original tumour. The walls of the cysts are formed by divisions of the splenic trabeculæ. It would appear that the tumour-cells had gained an entrance into the capsular veins of this area, where they had subsequently developed and finally broken down. No other changes of importance are noted in the spleen.

Remarks.—The tumour is in all probability a malignant hypernephroma, taking its origin from the adrenal cortex. It is alveolar in character, and from the intimate relationship of its cells to the blood-vessels it simulates closely the structure of a perithelioma. *April 4th*, 1905.

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20. *Obliterative arteritis.*

By William P. S. Branson.

Much as has been done to elucidate the affections of arteries, there is one group of conditions which, even in the matter of terminology and definition, is exceedingly obscure, the group, namely, that is comprised by the term "endarteritis obliterans." This will be borne in upon anyone who attempts to master the literature of the subject, and it is probable that this audience would provide a good many different definitions of the condition.

The term "obliterative arteritis" appears to have been introduced into medicine by Friedländer (1) in 1876 to describe what he calls "a widespread affection of the arterial system manifesting itself by the formation of a richly cellular connective tissue in the intima of medium-sized and small arteries, and leading . . . to complete obliteration by solid material." "This thickening," he says, "may progress to the density of pure fibrous tissue, or undergo transformation into a homogeneous refractive substance in which the elastic lamina is lost." . . . "We may make the general statement," he concludes, "that the constituents of the arterial wall, under suitable conditions of their surroundings, play a part in the great group of interstitial processes; an acute or chronic inflammation, or caseation in the supporting connective tissue of a vessel, will produce a corresponding process in the vessel wall, and this is very prone to manifest itself by a thickening of the intima."

The author of the term therefore clearly indicates a secondary involvement of arteries in a neighbouring inflammatory process.

Strangely enough, the bulk of cases referred to Friedländer's patronage are cases of apparently primary obliteration, not of terminal branches in tissues, but of main arteries to the extremities. This perversion of the term was due to von Wini-

warter (2), who in 1879 described a primary obliteration of the arteries of the feet in a man aged 57 years, and discovered in the affected vessels some histological resemblances to Friedländer's postulates. Subsequent writers followed his lead, with the result that for nearly twenty years the literature of "obliterative arteritis" is the literature of such apparently primary obliteration of the main arteries to the extremities, mostly in young adults, and often associated with gangrene, though the author specifically stated that, except in the physiological closure of the ductus arteriosus, the process was almost never primary. In about 1896 Thoma (3) expressed the opinion that the affection in question had no specific identity, and with his pronouncement this meteoric disease came to an end.

But though the manifest perversion of the term came to an end, the term itself has lived, but not, it seems, to much advantage, for authoritative opinion is to this day most discordant as to its proper use. To emphasise this fact it is only necessary to quote a few statements from current text-books.

Thoma (4) says that what von Winiwarter described as "obliterating arteritis" was an organised thrombosis in an artery.

Schmaus (5), speaking of intimal proliferation, says: "All these conditions are grouped as endarteritis obliterans," and details as items the closure of the ductus arteriosus, organisation of thrombi, and the obliteration associated with interstitial, syphilitic, tuberculous, and purulent affections.

Professor Coats (6) says: "Endarteritis obliterans is not an independent disease. It affects the finer vessels of certain organs, and consists, like atheroma, in a thickening of the intimal coat. It is seen especially in interstitial inflammations of organs, particularly chronic interstitial nephritis."

Of syphilitic arteritis he says: "There is considerable doubt as to the existence of a special gummatous arteritis as described by Heubner. A lesion of an artery is not be regarded as syphilitic unless it be either directly connected with a syphilitic lesion, or, in the absence of atheroma, is associated with syphilitic disease elsewhere."

Professor Sims Woodhead (7) says: "Endarteritis obliterans . . . occurs most frequently as—

(1) A syphilitic endarteritis.

(2) In healing wounds and interstitial inflammations.

Lazarus-Barlow (8) says: "Syphilitic inflammation affects the intima so constantly that the condition is called endarteritis, . . . syphilitic endarteritis, and endarteritis obliterans."

Finally, Ziegler (9) says: "The new connective tissue that develops in the substance of and replaces a thrombus owes its existence to proliferation of the cells of the vessel-wall. When the process leads to complete occlusion of the artery it is called endarteritis obliterans." Also he says: "Syphilitic arteritis is found either as an independent disorder or as part of a local affection. The former is not to be distinguished, either by the eye or with the microscope, from the arterial thickening due to non-syphilitic fibrous hyperplasia."

More opinions might be quoted, but here are enough to point out the disagreement of authorities. In one particular, however, they are all agreed, and that is, in refusing to give a monopoly in the term to the type of case recorded by von Winiwarter, which so long masqueraded as a specific morbid identity. For the rest it is clear that Lazarus-Barlow recognised in endarteritis a lesion pre-eminently syphilitic; that Professor Coats categorically denied the inference; that Ziegler, while admitting the existence of a syphilitic variety apart from gummatous infiltration, denied the possibility of histological differentiation between the syphilitic and other forms; that Thoma, Coats, Schmaus, and Woodhead embraced under the term every arteritis that obliterates, whether by aid of thrombosis or not. In the face of this disagreement let us consider a few common features of arteritis under the microscope. In practically all chronic arterial lesions it is fair to say that proliferation of the intima is a prominent feature. In atheroma it is the rule to find intimal proliferation associated with fatty or calcareous degeneration. In the cerebral arteritis associated with syphilis intimal proliferation is by far the most notable feature. Finally, in sections of granular kidney nothing is commoner than an endarterial proliferation of the terminals of the renal artery, leading to more or less complete obliteration of their lumina. Thus almost every common chronic arteritis has at one time or another the elements of obliteration, and it would seem that the term "obliterative arteritis," suggesting as it does a difference in kind, has little title to live, for the microscope shows only a difference of degree.

In view of these facts it would seem that there is only one

abiding distinction to be drawn between the various common forms of chronic arteritis—that is, between those in which the intimal proliferation is followed by fatty or calcareous degeneration (that is to say, atheroma) and those in which this tendency is absent, of which class syphilitic arteritis is the type. And even this cannot be conclusively maintained, for atheroma of large vessels is commonly found in association with intimal proliferations in the smaller ones, which show no tendency to break down, a fact suggesting that the same causal factors result differently in different situations. Still, syphilis does supply us with a lesion which may show no sign of breaking down, whether it affects the large arteries or the small ones—a lesion to which, more than to any other, the term "endarteritis obliterans" might with some justice be applied. The question I wish to ask to-night is whether a lesion widely distributed throughout the arterial system, limited almost entirely to the intima, and showing nowhere any tendency to fatty degeneration, is, as Lazarus-Barlow implies, a presumptive evidence of syphilis or not? and for this purpose I beg to submit the following details of a case in point.

A boy, aged 12 years, came recently under the care of Mr. H. Betham Robinson at the Hospital for Children, Shadwell, with the following history:

At the age of 4 years his gums began to hypertrophy. The overgrowth was removed, but recurrence took place within two months. His bodily health, however, was good until a few weeks before he came under notice, when he complained of a general aching and lost flesh. He had suffered from no specific fevers except measles and whooping-cough.

The boy was the third of a family of four children living. Two (the second and the sixth) had died of "bronchitis," aged 15 months to 2½ years respectively. The mother was dead of phthisis. She had had two miscarriages, but what relation they bore, in point of time, to the birth of the patient the father was unable to say.

The boy was well-nourished, with a rather depressed bridge to his nose, and greatly hypertrophied gums. His teeth barely protruded at all, but what could be seen of them appeared normal. All accessible arteries were thick and hard, and the pulse tension seemed high. The heart was hypertrophied, and there

was an apical systolic murmur. There was no œdema, and the urine contained a cloud of albumen and some hyaline and granular casts. Ten days after admission he began to be sick and developed the Cheyne-Stokes type of breathing. Shortly after he began to show signs of heart failure, with general anasarca and pleural effusion, and he died about six weeks after coming under notice.

The main facts of the autopsy are as follows: The hypertrophy of the gums proved microscopically to be a dense fibrous tissue. The lungs and pleuræ and pericardium showed no organic lesion. The heart was much hypertrophied and dilated, especially the left side, but there was no evidence of valvular disease. The left ventricle contained near its apex a small, decolourised, adherent clot, presumably *ante-mortem* in date of formation.

The aorta bore a few pale gelatinous projections on the intima, but no sign of atheromatous destruction. Under the microscope such a patch proved to be due to an intimal thickening dependent upon fibrillation of the internal elastic lamina, the new formation being but slightly cellular.

The brain and meninges were natural, but a few pial vessels showed whitish thickenings; these patches, like those on the aorta, proved microscopically to be a pure endarteritis, the middle and outer coats showing no change.

The basilar artery was the seat of an identical lesion. The condition of the kidneys was very remarkable. There was a great disparity in their size, the left kidney being considerably hypertrophied, the right equally shrunken, their length being as 3 to 2¼ inches. The right kidney in its lower half was reduced to a knob of fibrous tissue, the upper glandular half being no more than 1¼ inches long. The lower shrunken portion consisted of dilated calices covered by a layer of renal substance of little more than paper thickness. The glandular portion consisted of two well-formed pyramids covered by an abundant cortex. About the junction of the atrophied and glandular areas the surface was irregularly scored by deep furrows, as though a process of atrophy similar to that affecting the lower part were here commencing. The capsule stripped readily from the glandular surface, and left no granularity. Over the sclerotic districts the capsule was somewhat adherent. The renal artery was fully patent, and but little smaller than its fellow of the other side,

but its main branch to the atrophied area was distinctly reduced in size. The renal vein was blocked by a firm but not decolourised

FIG. 41.

A renal arteriole the lumen of which is much diminished from endarteritis.

thrombus. The ureter was patent, but its walls very thick and its lumen disproportionately small.

FIG. 42.

The renal artery of the same kidney; its structure is unaltered.

Microscopy of the upper, apparently natural, part of this kidney reveals no sign of nephritis, whether interstitial or parenchymatous, except in the neighbourhood of the hilum, where

there are some signs of patchy sclerosis attended by some obliteration of the arteries in the affected districts, partly by an endarteritis, partly apparently by pressure.

A section through the sclerotic lower part, taken at right angles to the entering vessels, has the following appearance:

There is considerable fibrosis, patchily distributed, strands of fibrous tissue alternating with renal substance in all stages of degeneration, from tubules almost normal to a condition of advanced sclerosis with cyst formation. In some of these sclerotic areas there is a good deal of small-celled infiltration, and in all a large number of arteries remarkably obliterated (Fig. 41). The obliteration affects the intima principally. In a typical instance the adventitia and media appear normal; immediately within the media is a deep layer of homogeneous hyaline material, pierced by spaces containing nuclei of many sizes and shapes, but few in number. Within this, again, and occupying the greater part of the lumen, is a fibrillar layer interspersed with nuclei inclined to be elongated, the whole being lined on its innermost surface by an intact endothelium. A section stained with acid orcein makes it appear that a great part of the proliferated intima consists of elastic fibres.

In marked contrast to this condition of the renal arterioles, the renal artery itself and also the branch to the atrophied area of the kidney show no lesion at all (Fig. 42).

The left kidney is enlarged in both its cortical and medullary elements. Its surface is scored in places by furrows similar to those previously described. The capsule strips readily except over the furrows, and leaves no granularity except for a few minute areas. The renal artery and vein and ureter are normal to the eye.

Microscopically, as to the naked eye, this kidney is in the main natural. Here and there is an arteriole affected by endarteritis similar to that above described, and the atrophic furrows are the regions in which the arterial lesion is most obvious. The renal artery on this side is slightly but distinctly affected by a fibrillation of the internal elastic lamina.

In neither of the kidneys was there any trace of amyloid degeneration. The spleen was hard but showed no scarring or deformity. Microscopically a number of the finest arterioles were found to be entirely obliterated by a fibrillar intimal overgrowth identical with that observed in the kidneys.

The liver was large, dark, and slightly "nutmeg" in character. Its hepatic arterioles were free from endarteritis, and the tissue showed no abnormality under the microscope.

The left ureter was natural, the right much thickened by a mingled fibrous and elastic overgrowth in its wall, but the arterioles of both ureters showed no disease.

The bladder was much hypertrophied, its walls being half an inch thick, and the vesical arterioles were free from disease.

Finally, the penis was the seat of marked phimosis, which possibly accounted for the hypertrophy of the bladder.

The radial and dorsalis pedis arteries were also examined. They both exhibited a well-marked circular proliferation of the intima, the elastic lamina remaining intact. The intima consisted of a dense layer of homogeneous material dotted with a few nuclei. The endothelium was not distinct, but remains of it could be seen in many places. The middle and outer coats were not appreciably affected.

Such are the facts of the case, and I beg to draw attention to the following three salient features which seem to mark the lesion as something apart from granular kidney, though the clinical symptoms were those of the latter disease:

(1) The extraordinary disparity in the size of the two kidneys.

(2) The gross localised sclerosis of the kidneys, without evidence of anything like a generalised interstitial inflammation; the intimate association of the sclerotic areas with local obliteration of the renal arterioles, and the absence of granularity of the surface.

(3) The existence of a widely diffused, but patchy, intimal proliferation throughout the arterial system, with no evidence anywhere of atheromatous breakdown.

These particulars seemed to justify an investigation of reported cases of granular kidney in childhood, a study which seems to show that whether or no these lesions are entitled to the name granular kidney, they have been present in a certain number of the cases so described. At the same time it must be admitted that the evidence is often chiefly circumstantial, and, therefore, inconclusive.

Gull and Sutton (10) in the paper originally describing arterio-capillary fibrosis, write as follows:

"Children are occasionally the subject of granular kidney. In the case of a girl, aged 9 years, the kidneys were much smaller

than normal, especially the left. One weighed two oz., the other 1¼ oz. The kidneys, in consequence of being greatly contracted, were much reduced in size, the surfaces very irregular and puckered and *not finely granular*. The heart's left ventricle was dilated and hypertrophied, but the valves healthy. The spleen was small and tough. Some of the arteries of the pia mater were much thicker than usual owing to the layer outside the muscular layer being much increased. The thickening was most marked in the capillary arterioles or larger capillaries, due to the formation of granular hyaline in the walls. The arterioles of the kidneys were much thickened by fibroid changes." This case, with the exception of the adventitial thickening of the pial arteries, is an almost precise parallel. The child was very young for granular kidney; the kidneys were distorted, furrowed, and not finely granular. Was it granular kidney?

Dakin (11) has communicated the case of a child, aged 2 years, in whom the left kidney only weighed 3 drachms, while the right weighed 2¾ oz. In the left kidney the cortex was much reduced, and there was microscopically an extreme degree of cirrhosis, but no mention is made of the arterial condition, either local or general.

Dickinson (12) describes the following case. A child, aged 12 years, who had suffered from scarlet fever some years before, came under notice for headache and vomiting, and died of cerebral hæmorrhage.

Post mortem the pial arteries were found atheromatous and much thickened in their muscular and fibrous coats. The left ventricle was much hypertrophied and its valves healthy.

The kidneys were very unequal in size. The left weighed 2 oz. The right weighed ½ oz. Of them he says: "The larger . . . . had thickened and adherent capsules, which when peeled off (a matter of some difficulty) left a level though not glossy surface, save that at about the centre of the gland was a somewhat reddish cicatricial depression. . . . The smaller kidney resembled the larger in character, though much more shrunk. It had the same thickened and well-nigh inseparable capsule, the same level but scarcely smooth surface. . . . Both pelves were large in relation to what remained of the kidneys, but neither of more than their natural capacity. The left ureter was slightly dilated. . . ."

It will be noticed that the pial arteries are described as

"atheromatous" which may or may not have been said in the strictest significance of the term, but on every other ground the case is a comprehensive parallel to that under notice.

Handford (13) recorded a case affecting a girl, aged 12 years, who had been through both measles and scarlet fever at the age of 3, the latter being followed by dropsy. She came under notice for vomiting, headache, and epileptiform fits—in a word, for uræmia.

Her right kidney weighed 2 oz., her left weighed only ½ oz. The capsules were adherent in places, the surface on their removal being smooth, except at areas of adhesion. "A marked contrast," he says, "to the contracted granular kidney." He calls the case one of "post-scarlatinal cirrhosis of the kidneys."

Another case is described by Ashby and Wright (14), a boy, aged 4 years, who died of uræmia after eight days' illness. The kidneys are described as small and shrivelled, weighing together 2 oz. Their capsules were adherent, their surfaces irregular, *not granular*, and pale. Yet another is recorded by Dr. Arthur Hall (15). A girl, aged 8 years, died with symptoms of uræmia and signs of granular kidneys. The kidneys were atrophied, each weighing less than one ounce, and the left was smaller than the right. The report on them runs as follows: "The *capsules stripped easily*, but left rough irregular surfaces having a coarsely granular appearance, with marked irregular pale areas of depression, some quite large. The quantity of cortical tissue was not regularly diminished, being almost entirely gone at some places, whilst hardly narrowed at all at others. The ureters were dilated on both sides, also the pelves and calices." Microscopy showed much fibrous tissue unevenly distributed, with marked thickening of the arterial intima.

Whatever be the truth about these analogous cases, it will probably be admitted by those who see the specimens under the microscopes that the lesions of the case under immediate notice are not the ordinary lesions of granular kidney. The fundamental lesion seems to have been an arterial one widely distributed about the system and culminating in the tissues of the kidneys and spleen. It was a proliferating endarteritis, and showed nowhere any atheromatous degeneration, and was histologically indistinguishable from the endarteritis of syphilis.

Hoche and Briquel (16), writing of tertiary syphilis, say it may

be distinguished from other renal disorders by the fact that it may be unilateral, or attack only a limited area of the kidney, and that it may give rise to cicatricial depressions similar to those found in the liver. Of late hereditary renal syphilis they say that it affects the type of a diffuse sclerosis, with or without amyloid degeneration.

With a view to the possibility of a syphilitic basis for the lesions of the present instance, a careful examination was made of the surviving immediate relatives of the boy.

The father is a robust man, aged 52 years. He positively denies that he has ever had syphilis, or that he ever exposed himself to venereal infection until the death of his wife. He shows no scars or other lesions suggestive of past syphilis.

The three living children are aged respectively 17, 11, and 9. None of them has ever had any ocular trouble, and in none of them are the features or teeth suggestive of hereditary syphilis. There remains the suspicious circumstance of the two miscarriages, and of these, as has been said, it is impossible to obtain the dates.

It is clear, therefore, that the evidence in support of a syphilitic origin for the lesions is of the vaguest, though it is tempting to assume a connection; it is also unfortunate that in none of the analogous cases is there any record of the family history; and thus for the present the etiology of the malady must remain speculative. But I venture to think that a case has been made out for considering this disease as something apart from granular kidney, and it is likely that a more complete investigation of cases of apparent granular kidney in children will reveal this pathological condition with some frequency, considering the rarity of the clinical condition as this period of life.

In conclusion, I have to thank Mr. H. Betham Robinson, Surgeon to the East London Hospital, for permission to make use of the case above related.

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December 6th, 1904.

21. *Obliterative arteritis, leading to gangrene of extremities in otherwise apparently healthy men in the prime of life.*

By E. MICHELS and F. PARKES WEBER.

IN a paper read at the Annual Meeting of the British Medical Association, in July, 1903,[1] we described two cases of obliterative arteritis in young men, leading to gangrene of the extremities. Of these cases the second was a complicated one; but the first was a typical one, affecting three limbs, in an otherwise apparently healthy man, aged 37 years, there being absolutely no evidence of syphilis, alcoholism, renal disease, saturnism, ergotism, or premature senility.

Our present case is remarkably similar in its main features, though only the two lower limbs have been affected.

The patient, Alexander H., a cigarette-maker, aged 39 years, a Jew from Roumania, was admitted into the German Hospital on August 3rd, 1904.

He formerly enjoyed good health, but at 23 years of age commenced to suffer from pain in the right lower extremity. The pain was in the foot and the muscles of the calf of the leg. It used to come on when he had walked for six or seven minutes, and was accompanied by muscular weakness, so that when the pain came on he had to stand still, but after two or three minutes it used to go better and he was able to go on for another six or seven minutes, and then stop again, and so on. Evidently this

[1] 'British Medical Journal,' September 12th, 1903, p. 566.

was a kind of "intermittent claudication" of the extremity.[1] He says the foot was quite red at that time, like it not rarely is in cases in which the blood supply is obstructed, owing to changes in the arteries of the affected limb.[2] At Riga, in 1889, after more than a year of these sufferings, the right lower extremity was amputated below the knee-joint. The wound healed rather slowly—that is to say, in about five months, and he then remained well till 1903. About June of that year he began to suffer from severe pains in the toes and calf of the left lower extremity, and he had a kind of "intermittent claudication" in that extremity, similar to that which he previously had had in the other. It was this trouble which brought him as a patient to the German Hospital.

There is not much more to be said in regard to the past history of the case. The patient had been moderate in alcohol, and there is not any history of venereal disease. He says, however, that he had been accustomed to smoke at least ten cigarettes a day, and has also taken a good deal of strong tea.

His father died at over 70 years of age, and his mother is still living, aged about 66 years.

Condition after admission (*August*, 1904).—The patient was a medium-sized, active man, without signs of disease in the heart, lungs, or abdominal organs. The urine showed nothing abnormal. There were no signs of any disease of the nervous system. The arteries and nutrition of the upper extremities seemed to be natural. Arterial pulsation could be felt in both inguinal regions, but pulsation was hardly, if at all, perceptible in the left popliteal artery (the right leg had been amputated in 1889, as already stated). Examination of the blood (October 6th, 1904) showed the hæmoglobin value to be about 100 per cent. of the normal standard; the number of red cells in the cubic millimetre was 5,120,000, and nothing remarkable was noticed in regard to the

[1] On the possible absence of cramp in "intermittent claudication" of extremities, see especially N. Ortner, "Zur Klinik der Angiosklerose," Volkmann's 'Sammlung Klinischer Vorträge,' Leipzig, 1903, No. 347, p. 865.

[2] Though this condition of redness and pain in a foot due to organic obstruction in arteries is in some respects "erythromelalgia-like" it is probably not identical with that met with in "idiopathic" or "neuropathic" erythromelalgia—see F. P. Weber, "A Case of Erythromelalgia, illustrating its Relation to Raynaud's Symptom-Complex," 'British Journal of Dermatology,' February, 1904, p. 70.

white corpuscles. Ophthalmoscopic examination (October, 1904) showed nothing abnormal.

On account of gangrene, Dr. Michels first of all removed the left big toe on August 5th, 1904. The wound did not heal properly, and intolerable pain in the foot[1] continued, so that on October 7th, 1904, Dr. Michels, at the patient's repeated request, other treatment having been found useless, amputated the left lower extremity below the knee. At the operation there was hardly any bleeding from the cut vessels, and on examination it was found that the lumen of the popliteal artery was completely obliterated at the site of amputation.

Before we come to the microscopic examination of the vessels and nerves and muscles of the amputated extremity, we must mention that the progress of the case was quite uneventful. The patient was free from pain after the operation and the wound healed well. In December the stump appeared a good one, although at one part he said it was tender to pressure. His general health was good. It may be noted that the general arterial blood-pressure was not in March, and probably never had been, diminished. On March 23rd it was about 145 mm. mercury in both arms, according to the Riva-Rocci apparatus.

Microscopic examination.

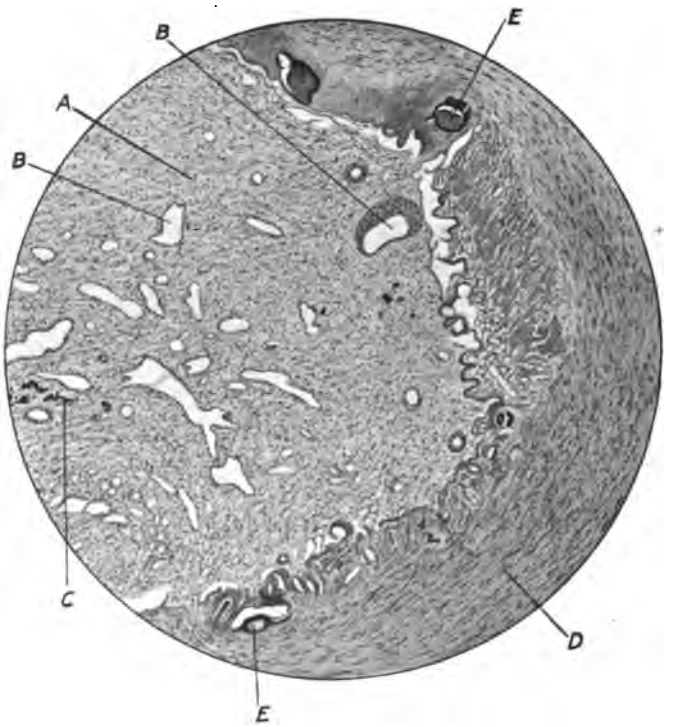
Sections were made, (1) of the popliteal vessels and nerve, from behind the tibia; (2) of the anterior tibial artery, with accompanying veins and nerve; (3) of the dorsalis pedis artery and vein, and the nerves accompanying them: (4) of a piece of muscle from the inner side of the first metatarsal bone.

(1) *Popliteal vessels and nerve.*—The artery (see Fig. 43) appeared so small in section as to suggest the presence of congenital hypoplasia. It was found to have its lumen obliterated by fairly dense connective tissue, containing a great number of newly formed blood-vessels, and a certain amount of pigment granules, doubtless derived from blood (hæmosiderin), and probably indicating that part of the connective tissue obliterating the arterial lumen was the result of organisation of a thrombus. The

[1] According to the patient when the trouble had lasted a long time the pain was more severely felt in the foot than in the calf of the leg.

elastic lamina of the internal coat was well preserved, and at some parts of the wall it was doubled. At some parts also there was a certain degree of proliferative endarteritis. Close outside the elastic lamina there were several minute points of calcification which could be dissolved out by weak acids, and in prepar-

FIG. 43.



Transverse section of part of the popliteal artery (× 60) showing its channel obliterated by connective tissue (A). In this are many newly-formed blood-vessels (B) and in some parts groups of brown pigment granules, some of which are represented diagrammatically in black (C). D = the middle coat. There are some small areas of calcification (E) just outside the elastic lamina, which is not very distinctly seen in the section illustrated.

ing the sections it was noted that there seemed to be gritty particles cut through by the microtome. The vasa vasorum were natural. One of the two veins accompanying the artery showed (in transverse section) a certain amount of "apparent thickening," due, as usual, to longitudinally arranged un-

striped muscle-fibres imitating proliferative changes of the inner coat.[1] The nerve appeared normal.

(2) *Section of the anterior tibial vessels and nerve.*—The artery was occluded by connective tissue, similar to that noticed in the popliteal artery, and almost certainly the result of organisation of a thrombus. The elastic lamina was distinct, and very wavy in outline. One of the veins showed a considerable amount of the "apparent thickening" due to longitudinally arranged muscle

FIG. 44.

Transverse section of the dorsalis pedis artery (× 60), showing the lumen contracted and nearly obliterated by proliferative endo-arteritis. The greatly thickened inner coat, bounded externally by the clearly-defined wavy elastic lamina, consists chiefly of connective tissue containing many newly-formed blood-vessels. No pigment granules are seen in it.

fibres imitating proliferation of its inner coat—that is to say, when seen in transverse section.[1] The nerve appeared normal.

(3) *Section of the dorsalis pedis vessels and nerve.*—The artery

[1] *Vide* F. Parkes Weber, "An Apparent Thickening of Subcutaneous Veins." 'Journal of Pathology and Bacteriology,' May, 1899, p. 73.

(see Fig. 44) showed an extreme degree of endarteritis proliferans, so that its lumen was greatly contracted, but not completely occluded. Much of the thickened inner coat had been converted into connective tissue by a process of organisation, with formation of new blood-vessels. The elastic lamina was deficient at one part. The vein and nerves appeared normal.

(4) *Section of the muscle.*—The muscle-fibres throughout showed complete absence of transverse striation, and the presence of very marked fibrillation, indicated by the longitudinal striation. There seemed to be excess of nuclei in the connective tissue in some parts.[1]

We must here mention that we are indebted to Dr. Mülberger, one of the house-surgeons of the German Hospital, for some of the sections, and we have to thank Mr. S. G. Shattock and Dr. F. E. Batten for their kindness in examining the sections with us, the latter especially in regard to the condition of the muscle and nerves.

Remarks.

The pathology of this affection has been so ably studied by F. von Winiwarter,[2] C. Sternberg,[3] A. A. Wwedensky,[4] W. von Zoege-Manteuffel,[5] Bunge,[6] P. Wulff,[7] O. von Wartburg,[8] and Pearce Gould;[9] and the literature and views of various authors have been so recently discussed by Bunge and von Wartburg that we need not enter on these matters at length. Cases have also been described in England by Pearce Gould,[10] W. B.

[1] On "ischæmic" changes in striped muscles—that is, those due to arterial obstruction—see H. Lorenz's "Muskelerkrankungen," in Nothnagel's 'System,' Vienna, 1898, pp. 62 *et seq.*

[2] "Ueber eine eigenthümliche Form von Endarteritis und Endophlebitis mit Gangrän des Fusses," 'Arch. f. klin. Chir.,' Berlin, 1879, vol. xxiii, p. 202. In C. Friedländer's original paper on "Arteritis Obliterans," 'Centralbl. f. d. med. Wissenschaft,' January 22nd, 1876, the process was discussed with no special reference to cases like the present one.

[3] 'Wien. klin. Woch.,' 1895, Nos. 37 and 39.

[4] 'Arch. f. klin. Chir.,' 1898, vol. lvii, p. 98.

[5] 'Arch. f. klin. Chir.,' 1891, vol. xlii, p. 569, and 'Deut. Zeit. f. Chir.,' 1898, vol. xlvii, p. 461.

[6] 'Arch. f. klin. Chir.,' 1901, vol. lxiii, p. 467.

[7] 'Deut. Zeit. f. Chir.,' 1901, vol. lviii, p. 478.

[8] 'Beiträge z. klin. Chir.,' 1902, vol. xxxv, pp. 656 to 670.

[9] The second Lettsomian Lecture, 'Lancet,' 1902, vol. i, p. 717.

[10] 'Clin. Soc. Trans.,' vol. xvii, p. 95, and vol. xxiv, p. 134, and 'Lancet,' *loc. cit.*

Hadden,[1] W. G. Spencer,[2] A. Dunlop,[3] and (a doubtful and complicated case) J. A. Arkwright.[4] In France, R. H. Camusat[5] has recently considered the subject, and J. Darier has shortly alluded to it in his work on 'Syphilitic Arteritis.'[6]

As to whether the final occlusion of arteries in these cases is generally due to thrombosis in already diseased vessels or to mere proliferation of the intima without thrombosis, opinions still differ. The question is, we believe, not a very important one, and we doubt whether, when thorough organisation has taken place, it is always possible to distinguish between the two processes. In our present case, however, there can be practically no doubt that the occlusion of the larger arteries was due to thrombosis. If we had examined merely the popliteal vessels, we could hardly have connected the affection with arteritis obliterans, and should have merely come to the conclusion that the artery had in some way or other become thrombosed. The dorsalis pedis artery showed great thickening and vascularisation of the intima, but to what extent this change preceded the clotting in the popliteal artery it is difficult to say. It is quite possible that the onset of the pains in the foot and calf of the leg and the intermittent claudication were brought about by clotting in the popliteal artery.

The disease occurs almost exclusively in the male sex, and the lower extremities are chiefly affected. Both in this and in our previous case the patients were poor Jews, living in the East End of London, as far as we can ascertain free from syphilis, alcoholism, and premature senility, but both of them accustomed to smoke at least ten cigarettes daily, and to drink a good deal of tea. We state this for what it is worth, and do not mean to hint that tobacco would induce this affection in most ordinary persons. It might, however, we believe, help to induce the affection in predisposed individuals. But the question then arises, What constitutes such a predisposition, and could a certain hypoplasia of arteries be connected with it? We have not sufficient data at

[1] 'Clin. Soc. Trans.,' vol. xvii, p. 105.
[2] 'Clin. Soc. Trans.,' vol. xxxi, p. 89.
[3] 'Lancet,' 1903, vol. i, p. 1440.
[4] 'Lancet,' 1902, vol. ii, p. 737. See also the editorial article on p. 753.
[5] "L'artérite dite spontanée," 'Thèse de Paris,' 1902.
[6] 'De l'Arterite Syphilitique,' Paris, 1904.

present to discuss this question, but in the present case the popliteal artery seems to have been originally rather small.

It is possible that both poor or unwholesome food (ergotism is, of course, unknown in England) and racial factors may play a part in the etiology. We know of this disease at present commencing in a third poor East End Jew in London. It is curious that we have during the last few years met with three instances of so rare a disease, and the fact that in all three of these instances the patients have been East End Jews between the ages of 30 and 40 years suggests the existence of a racial or social (habits in regard to food and hygiene) predisposition. In a discussion at the Berlin Medical Society on November 9th, 1904, Professor J. Israel referred to an idiopathic gangrene of the lower extremities, occurring in men between 30 and 40 years of age, especially Russian Jews. This had attracted attention, not only at Berlin, but likewise at Königsberg and Dorpat.

Addendum.

Since this paper was written our colleague, Dr. Zum Busch, has kindly brought to our notice a case of commencing gangrene in the foot of an otherwise apparently healthy Russian Jew, aged 30 years, at present under his care at the German Hospital. The patient is a worker in a cigarette-factory, and has been accustomed to smoke several cigarettes daily, which, owing to his employment, he has, like our patient A. H., been able to obtain without paying for them.

April 4th, 1905.

22. *The vitality of the typhoid bacillus in shellfish.*

By E. KLEIN, F.R.S.

THE following tables contain a summary of the results of six separate series of experiments. These were made in order to ascertain the behaviour of the *Bacillus typhosus* in oysters, cockles, and mussels, either when these were separately and directly infected with a definite quantity of the microbe or when they were kept for twenty-four hours in sea water previously infected with a definite quantity of the microbe:

EXPERIMENT I.

Clean Burnham oysters. Each oyster received into the interior of the shell a little over 160,000,000 of *B. typhosus*. Half of the number of these oysters was then placed in clean sea water which was changed every twenty-four hours; the other half was not placed in sea water at all, but was kept "dry" in a cool chamber. The first lot will be designated "wet oysters," the other lot "dry oysters."

Each oyster received over 160,000,000 B. typhosus.

Lot 1.—*Wet oysters.*

Oyster	1	After 1 day	70,000	*B. typhosus*	per oyster.
„	3	„ 2 days	9100	„	„
„	5	„ 3 „	1100	„	„
„	7	„ 4 „	320	„	„
„	9	„ 6 „	0	„	per $\frac{1}{10}$ part oyster.
„	11	„ 7 „	0	„	„ $\frac{3}{10}$ „

Lot 2.—*Dry oysters.*

Oyster	2	After 1 day	1,200,000	*B. typhosus*	per oyster.
„	4	„ 2 days	175,000	„	„
„	6	„ 3 „	42,000	„	„
„	8	„ 4 „	3700	„	„
„	10	„ 6 „	40,000	„	„
„	12	„ 7 „	1220	„	„

EXPERIMENT II.

Clean Colchester oysters were placed in sea water; in this water typhoid bacilli of culture were distributed to the amount of 744,000 *B. typhosus* per 1 c.c. Twenty-four hours after, oyster 1 was analysed and found to contain in its body 40,000 *B. typhosus*. Then the oysters were separated into two lots, lot 1 being placed in fresh, clean sea water, which was changed every twenty-four hours; lot 2 was kept "dry" as above.

Oyster 1 *after twenty-four hours in infected sea water,* 40,000 *B. typhosus.*

Wet oysters.

Oyster	3	After	1	day	in clean water,	1380	*B. typhosus*	per oyster.
„	5	„	2	days	„	440	„	„
„	7	„	5	„	„	82	„	„
„	9	„	6	„	„	44	„	„
„	11	„	7	„	„	0	„	„
„	13	„	9	„	„	0	„	„

Dry oysters.

Oyster	2	After	1	day	dry .	40,000	*B. typhosus*	per oyster.
„	4	„	2	days	dry .	3700	„	„
„	6	„	3	„	.	700	„	„
„	8	„	5	„	.	150	„	„
„	10	„	6	„	.	280	„	„
„	12	„	7	„	.	510	„	„
„	14	„	9	„	.	90	„	„

EXPERIMENT III.

Of Experiment II, ten oysters (six wet, four dry) were left over. These, there was reason to suppose, had become practically free of *B. typhosus*, with which they had been originally infected. Both lots, wet and dry, were then kept for several days in clean sea water, and were then transferred to sterile sea water, to which culture of *B. typhosus* was added to the amount of 2,250,000 *B. typhosus* per 1 c.c. After twenty-four

hours the number of *B. typhosus* was determined of the sea water and of one oyster of each lot, *i.e.* of the lot 1 "previously wet" and of lot 2 "previously dry." The sea water was then changed every twenty-four hours.

Sea water.

Immediately after infection .	2,250,000 *B. typhosus*	per 1 c.c.	
1 day after infection . .	126,000	„	„
„ change . .	250	„	„
2 days after „ . .	0	„	per $\frac{1}{10}$ c.c.
3 „ „ . .	0	„	„
4 „ „ . .	0	„	„
6 „ „ . .	0	„	„

Previously wet oysters.

Oyster 15—After 1 day .	84,000 *B. typhosus*	per oyster.	
„ 17 „ 2 days .	935	„	„
„ 19 „ 3 „ .	105	„	„
„ 21 „ 4 „ .	0	„	per $\frac{1}{10}$ part oyster.
„ 23 „ 7 „ .	0	„	„ „
„ 25 „ 8 „ .	0	„	„ „

Previously dry oysters.

Oyster 16—After 1 day . .	1,318,000 *B. typhosus*	per oyster.	
„ 18 „ 2 days. .	1900	„	„
„ 20 „ 3 „ . .	646	„	„
„ 22 „ 4 „ . .	713	„	„

EXPERIMENT IV.

Polluted oysters from the foreshore of Southend-on-Sea. The outside of the shell was well brushed and cleaned, and the oysters were then placed in sterile sea water in a tub, to which culture of *B. typhosus* was added to the amount of 2,470,000 *B. typhosus* per 1 c.c. In this infected water the oysters remained for twenty-four hours; then the sea water of the tub was tested, as also one oyster. The oysters were then taken out, the tub was well cleaned, and received fresh sterile sea water. The oysters were divided in two lots. Lot 1 were replaced in the clean sea water

—"wet oysters." Lot 2 were not replaced in sea water, but were kept "dry" in a cool chamber. The sterile sea water was changed frequently.

Sea water.

Immediately after infection .	2,470,000	*B. typhosus*	per 1 c.c.
24 hours after infection . .	1,530,000	„	„
1 day after change. . .	13,180	„	„
2 days „ . . .	10,580	„	„
4 „ „ . . .	20	„	„
6 „ „ . . .	0	„	per $\frac{1}{10}$ c.c.
8 „ „ . . .	0	„	„

Wet oysters.

Oyster 1—After 1 day in infected water	95,800	*B. t.*	900	*B. coli.*
„ 3 „ 2 days in clean „	752,800	„	no	„
„ 5 „ 4 „ „	1200	„	„	„
„ 7 „ 6 „ „	200	„	„	„
„ 9 „ 7 „ „	378	„	„	„
„ 11 „ 8 „ „	56	„	„	„
„ 13 „ 9 „ „	390	„	„	„
„ 15 „ 11 „ „	0	„	per $\frac{1}{8}$ part of oyster.	

Dry oysters.

Oyster 2—After 2 days dry .	58,700	*B. typhosus.*	No *B. coli.*
„ 4 „ 4 „ .	17,400	„	„
„ 6 „ 6 „ .	37,900	„	„
„ 8 „ 7 „ .	1300	„	„
„ 10 „ 11 „ .	oyster looked abnormal, shell closed very slowly.		

. Innumerable *B. typhosus*, very large number of *B. coli.*

EXPERIMENT V.

Several dozen cockles were placed in sea water previously infected with *B. typhosus* of culture to the amount of four millions per 1 c.c. After twenty-four hours the cockles were taken out and washed: two were retained for analysis, the rest were

transferred to clean sand wetted with clean sea water. This change—viz. placed into clean sand wetted with clean sea water —was repeated several times in the course of ten days.

The two cockles above referred to, which were examined twenty-four hours after having been kept in the typhoid-infected sea water, showed that each contained in its body about half a million of *B. typhosus* (120 *B. coli*).

Cockles 1 and 1*a*, after twenty-four hours in infected water, contained each about 500,000 *B. typhosus*.

Cockle 2, after one day's change, contained 153,000 *B. typhosus* (no *B. coli*).

„ 4, after two days' change, contained 382,000 *B. typhosus* (no *B. coli*).

„ 6, after five days' change, contained 358,000 *B. typhosus*.

„ 8, „ six „ „ 1,541,000 „

„ 10, „ seven „ „ 138,600 „

„ 12, „ nine „ „ 69,300 „

„ 12*a*, „ nine „ „ 111,000 „

„ 14, „ ten „ „ 1600 „

„ 14*a*, „ ten „ „ 69,000 „

Cockle 14 was not quite normal; its shell did not close well.

Experiment VI.

Several dozen mussels were placed in sea water infected with *B. typhosus* of culture to the amount of 5,170,000 *B. typhosus* per 1 c.c.

Having been kept for twenty-four hours in the infected sea water, the mussels were washed in clean sea water: one was kept back for analysis, the remainder were transferred to a fresh clean tub with sterile sea water covered with seaweed. In this water the mussels remained for about six hours, after which time the bulk of the water was poured off, leaving just sufficient to keep the mussels in the tub in a wet condition. By doing this we tried to imitate to some extent what occurs under natural conditions—viz., mussels are not permanently immersed in the water like oysters, but during ebb remain uncovered by water. This same process—viz. clean tub with fresh sterile sea water for six hours—was repeated every twenty-four hours as long as any of the mussels remained alive.

Mussel 1 (large), kept in infected sea water for twenty-four hours, contained over 6,000,000 *B. typhosus*.

„ 2 (medium), one day after change, contained 74,800 *B. typhosus*.

„ 3 (large), two days after change, contained 628,660 *B. typhosus*.

„ 4 (medium), three days after change, contained 36,000 *B. typhosus*.

„ 5 (medium), five days after change, contained 58,450 *B. typhosus*.

„ 6 (medium), six days after change, contained 6250 *B. typhosus*.

„ 7 (medium), seven days after change, contained 14,200 *B. typhosus*.

All these mussels were in good condition, looked in every way normal, shell well closed. The experiment could not be continued on account of the difficulty of keeping them alive and normal.

Having explained the scope of the inquiry, and the methods for determining in a given oyster and other shell-fish (mussel and cockle) at a given period the number of *B. typhosus*, as also of *B. coli communis*, with which the shell-fish had been supplied, the author summarises his results thus:

(1) Oysters readily take up into their interior the *B. typhosus* which had been introduced into their shell or into the surrounding sea water.

(2) Oysters, clean at starting, rapidly clear themselves of the ingested *B. typhosus* if they are kept in clean sea water which is frequently changed.

(3) Oysters, clean at starting, clear themselves of the ingested *B. typhosus* to a less extent and slower if they are kept in a "dry" state—*i. e.* out of the sea water.

(4) Oysters from a polluted locality clear themselves of the ingested *B. typhosus* to a less extent and at a slower rate, even if kept in clean sea water, than oysters clean at starting.

(5) Oysters from a polluted locality retain the ingested *B. typhosus* to a markedly larger extent if kept "dry"—*i. e.* outside the water.

(6) The process of "clearing themselves" of the ingested *B. typhosus* cannot be owing to the oyster merely "passing out"

the ingested *B. typhosus*, but must be due to a large extent to an inherent power of the oyster of *directly devitalising the microbe*. The experiments with the "dry" oysters prove this, and it is also evident from the rapid rate at which this microbe disappears from the oysters kept in clean water if compared with the very small number of the microbe (*B. typhosus*) found at the same time in the surrounding sea water (Experiments III and IV).

(7) Oysters which had been infected with *B. typhosus*, and which were then kept in a "dry" state till they had practically cleared themselves of the microbe, when subjected to re-infection with *B. typhosus* are less capable of dealing with this microbe, even if they are kept in clean sea water, than the re-infected oysters which had always been kept in the water. This could be explained by the obvious supposition that oysters by being kept for some days out of the water are not possessed of the same degree of vitality and activity of their tissues as oysters are which have always been kept under normal conditions—*i. e.* in water.

(8) Oysters from a polluted locality, and containing a large number of *B. coli*, very rapidly clear themselves of this microbe, both those kept in as also those kept out of the water. This shows that *B. coli* is foreign to the oyster and is rapidly destroyed by it.

(9) However largely infected with the *B. typhosus*, the oysters at no time present to the eye any sign of such infection; they remain in all parts normal in aspect. This is the case not only with the infected oysters kept in sea water, but also with the infected oysters kept in the "dry" state. There was only one exception—viz. an oyster derived from a polluted locality, which oyster had been eleven days out of the water.

(10) During the time of these experiments (part of September, October, and part of November) the oysters lived quite well in *sterile* sea water frequently changed. There was no alteration noticeable in the aspect of the fish; they remained plump and juicy, and capable of promptly and tightly closing the shell.

(11) Cockles readily embody the *B. typhosus* present in the sea water. While the number of these latter appears at first to diminish in the body of the cockles, it soon increases to a considerable degree, for five days after the cockles had been removed from the infected water and kept in clean sand the number of

B. typhosus exceeded three times the number initially present. Their subsequent diminution proceeded only slowly, since even ten days after their removal from the infected water the cockle examined still contained in its body 69,000 *B. typhosus*.

(12) Mussels also readily embody the *B. typhosus*; in fact, the analysis seems to show that mussels do so to an extent greater than oysters or cockles. As regards the fate of the *B. typhosus* in the mussels, these appear to stand between oysters and cockles, since in mussels the *B. typhosus* undergoes gradual diminution, but this diminution is incomparably slower than in oysters, but takes place somewhat quicker than in cockles.

(13) Experiments were made by placing clean oysters—free of *B. coli*—in sea water previously infected with normal human fæcal matter, or with domestic sewage, of which the number of *B. coli communis* was ascertained. It was found that while the oysters readily ingest the *B. coli communis*, they as readily clear themselves of this microbe if afterwards placed and kept in clean sea water. From which it follows that just as the *B. typhosus* so also the *B. coli communis* is a microbe alien to the oyster, and when present in it must have been derived from the surroundings.

April 18th, 1905.

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23. *Experiments on the grafting of the thymus gland in animals.*

By Leonard S. Dudgeon and A. E. Russell.

We undertook these experiments with the idea of observing whether grafting of the thymus gland would produce any alteration in the character of the blood in animals, and whether we should be able to produce a condition in any way resembling lymphatism, in which the thymus gland is known to play such a prominent part.

We may state at the outset that we failed to produce either of these conditions as a result of our attempts to graft this gland; but in the case of two dogs both lymphatism and severe changes in the blood occurred, but due to an entirely different cause.

We attempted grafting the thymus gland into the peritoneal cavity of animals of the same species and of the same litter as

those from which we had obtained the gland, but in every instance the "grafts" rapidly degenerated. One kitten, one rabbit, and four puppies were used for the experiments. Control animals were also used.

The blood.—The examination of the blood included the enumeration of red blood corpuscles and of leucocytes; the estimation of the percentage of hæmoglobin and of the colour index, the examination of the fresh blood, and a differential count of 500 leucocytes obtained from film preparations of the blood, stained by Leishman's method.[1]

CAT A.—*Small tabby kitten, weight* 1900 *grms. Intra-peritoneal graft of thymus of kitten of same litter. Operation, June* 12*th,* 1903.

	June 18th.	June 20th.	June 30th.	July 7th.	July 27th.	Aug. 26th.
Red cells	5,276,000	5,553,125	—	7,359,375	7,706,250	8,000,000
Hæmoglobin	65	75	75	80	90	110
Colour index	0·65	0·7	—	0·54	—	—
Leucocytes	6920	9480	15,460	3960	7960	4220
Differential count	**Per cent.**	**Per cent.**	**Per cent.**	**Per cent.**	**Per cent.**	**Per cent.**
Polynuclear neutrophile cells	53·2	52·8	65·8	63	48·5	72·4
Small lymphocytes	21·4	30	20·6	16	26·6	19
Large „	3·6	5·8	4·2	7·4	8	1·8
Large hyaline cells	6·8	5·4	0·8	7·4	3·5	2·6
Transitional „	0·6	1·2	0·2	2	—	—
Polynuclear eosinophiles	14·4	4·8	8·4	4·2	13	4·2
	Per c.mm.	**Per c.mm.**	**Per c.mm.**	**Per c.mm.**	**Per c.mm.**	**Per c.mm.**
Polynuclear neutrophile cells	3681	5005	10,200	2495	3858	3059
Small lymphocytes	1480	2844	3193	634	2121	803
Large „	249	550	653	293	636	76
Large hyaline cells	470	512	124	293	278	110
Transitional „	996	455	31	79	—	—
Polynuclear eosinophiles	41	114	1302	158	1060	177

[1] In all our investigations on the blood, we use a preparation of Professor Leishman's stain, about three times as strong as his.

In the tables we have given the number of each variety of leucocyte in percentage and per cubic mm. of blood.

A complete *post-mortem* examination was made on each animal. The tissues were fixed in alcohol, 10 per cent. formalin, and in Orth's fluid immediately after death.

Sections of the bone-marrow and of all the viscera, except the brain and spinal cord, were stained by numerous methods (hæmalum and eosin, van Gieson's stain, Leishman's eosin-methylene blue, ferrocyanide of potassium and hydrochloric acid).

Notes on blood of cat A.—A slight stitch abscess formed in this case, but the wound was quite healed on June 20th, *i. e.* eight days after the operation.

June 12th.—One normoblast was seen while counting 500 leucocytes, otherwise the red cells were normal.

June 20th.—No abnormal leucocytes or red cells seen.

June 30th.—Red and white cells appear to be normal.

July 7th.—One normoblast seen.

July 27th.—Red and white cells normal in shape, size, and staining reactions.

August 26th.—Slight polychromatophilic degeneration, otherwise the red cells were normal.

Post-mortem examination was made six months from the day of operation. There was no evidence of rickets, and every viscus appeared to be normal. The thymus gland weighed 3·400 grms. There were three pieces of what appeared to be grafted thymus gland in the peritoneal cavity: two pieces were attached to the rectum and one to the great omentum. Sections of these masses, however, failed to show a trace of glandular tissue, and showed only fibrous and adipose tissue.

RABBIT I.—*Weight* 1290 *grms. Intra-peritoneal grafting of thymus gland from another rabbit. Weight of thymus gland grafted* 2·21 *grms. Operation, March 8th,* 1904.

	March 9th.	March 16th.	March 28th.
Red cells . .	6,400,000	6,200,000	5,993,750
Hæmoglobin .	100%	100%	85%
Colour index .	0·8	0·8	0·72
Leucocytes . .	2040	4860	2800

RABBIT I—*continued.*

Differential count	March 16th. Per cent.	March 28th. Per cent.	March 16th. Per c. mm.	March 28th. Per c. mm.
Polynuclear cells	48·5	42·5	2357	1190
Small lymphocytes	29·5	35·5	1423	994
Large „	9·0	9·0	437	252
Large hyaline cells	2·5	2·5	121	90
Finely basophilic cells	5·25	3·5	255	98
Amphophilic cells[1]	1·0	2·75	48	77
Polynuclear eosinophiles	4·25	4·25	206	119

Notes on blood. March 16th.—Two normoblasts seen. Slight polychromatophilic degeneration present.

March 28th.—Ditto.

Post-mortem examination, five weeks from date of operation. No evidence of rickets. All viscera appear to be normal. Weight of thymus gland, 2·720 grms. No evidence of grafted thymus gland in peritoneal cavity.

DOG D.—*Brown pup, weight* 1307 *grms. Intra-peritoneal graft from two puppies of the same litter. Combined weight of thymus glands used for grafting was* 12·14 *grms. Operation, February* 22*nd,* 1904.

			Control dog (same litter). Weight 1366 grms.	
	Feb. 29th.	March 9th.	Feb. 29th.	March 9th.
Red cells	4,000,000	3,425,000	—	3,500,000
Hæmoglobin	60%	50%	70%	62%
Colour index	0·75	0·73	—	0·8
Leucocytes	14,300	11,500	12,500	11,980
Differential count	**Per cent.**	**Per cent.**	**March 3rd. Per cent.**	**March 29th. Per cent.**
Polynuclear neutrophiles	61	63·4	61	52·6
Small lymphocyte	7·6	9·4	16	17·4
Large „	7·4	7·2	9·4	8
Large hyaline cells	15·2	10·4	6·6	14·6
Transitional „	4	4·2	0	3·2
X-cells[2]	2·4	3·2	1·4	2·8
Polynuclear eosinophiles	2·4	2·2	5·4	1·4

[1] These cells, by Leishman's method, appear to have both basophilic and eosinophilic (slight) granules.

[2] The X-cell has a nucleus very similar to the nucleus of the polymorphonuclear neutrophil except that the extremities are "lobed"; the cytoplasm is non-granular and basophilic.

Dog D—*continued.*

			Control dog (same litter) Weight 1366 grms.	
	Feb. 29th. Per c. mm.	March 9th. Per c. mm.	March 3rd. Per c. mm.	March 29th. Per c. mm.
Polynuclear neutrophiles	8723	7291	7320	—
Small lymphocytes	1086	1081	1944	—
Large „	1058	826	1128	—
Large hyaline cells	2173	1196	792	—
Transitional „	572	483	—	—
X-cells	343	368	168	—
Polynuclear eosinophiles	343	253	648	—

Notes on blood of dog D. February 29th.—Polychromatophilic degeneration, macrocytes, microcytes, and poikilocytes seen.

March 3rd.—The same changes in the red cells as on the previous date, also four normoblasts seen.

Control animal, March 9th.—Two normoblasts present.

Control animal, March 29th.—The same changes in the red cells as on the previous date.

Animal was killed under anæsthesia five weeks from date of operation. There was no evidence of rickets and all the viscera appeared to be normal. The thymus gland weighed 2·50 grms. One large nodule of what appeared to be a portion of grafted thymus gland was found attached to the great omentum, but this nodule consisted entirely of fibrous and adipose tissue.

Dog F.—*Brown pup, weight* 1325 *grms. Intra-peritoneal graft from two puppies of the same litter. Combined weight of thymus glands used for grafting,* 8·5 *grms. Operation, May* 16*th*, 1904.

	Before operation. May 15th.	After operation. May 24th.	Before operation. May 15th.	After operation. May 24th.
Red cells	4,800,000	5,150,000		
Hæmoglobin	65%	62%		
Colour index	0·6	0·6		
Leucocytes	10,700	18,016		
Differential count	Per cent.	Per cent.	Per c. mm.	Per c. mm.
Polynuclear neutrophiles	53·4	59·4	5713	10,692
Small lymphocytes	31·4	30·2	3360	5436
Large „	4·8	2	514	360
Large hyaline cells	5·4	4	578	720
Transitional „	3·8	1·4	407	252
X-cells	0·8	1	86	180
Polynuclear eosinophiles	0·4	2	43	360

Notes on blood of dog F. May 15th.—One megaloblast and three normoblasts seen while counting 500 leucocytes. Well-marked polychromatophilic degeneration; numerous macrocytes, microcytes, and poikilocytes seen.

May 24th.—One megaloblast but no normoblasts seen, otherwise as above.

Dog was killed accidentally ten days from date of operation. The animal was perfectly healthy. Pieces of thymus gland were attached to the abdominal wall, great omentum, and to the colon.

Microscopical examination.—Sections were stained with hæmalum and eosin, and by van Gieson's method. The grafted gland was found to be degenerated; the degenerated tissue was infiltrated with round cells and polynuclear cells, and there was a wall of fibrous tissue around.

Dog G.—*Pup, weighing* 1000 *grms. Intra-peritoneal graft from two puppies of the same litter. Combined weight of grafted thymus glands,* 9·43 *grms. Operation, May* 31*st.*

	Before operation.	After operation.			
	May 30th.	June 4th.	June 11th.	June 22nd.	Aug. 15th.
Red cells. . . .	4,659,375	4,294,250	4,200,000	4,700,000	—
Hæmoglobin . . .	70%	65%	72%	75%	—
Colour index . . .	0·78	0·75	0·85	0·7	—
Leucocytes . . .	11,400	11,940	8100	7000	3380
Differential count	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.[1]
Polynuclear neutrophiles	50·4	58·8	58·8	41·8	45
Small lymphocytes. .	38·4	30	31·6	31·6	36
Large „ . .	6·6	4·8	3	16	2
Large hyaline cells .	2·2	2·2	2·6	5·8	2
Transitional cells . .	1·2	2	2·4	0·8	—
X-cells	1	1·4	1·6	3·4	1
Polynuclear eosinophiles	0·2	0·8	—	0·6	9
	Per c. mm.	Per c. mm.	Per c. mm	Per c. mm.	Per c. mm.
Polynuclear neutrophiles	5746	7056	4763	2926	1521
Small lymphocytes. .	4378	3600	2560	2212	1216
Large „ . .	752	576	243	1120	68
Large hyaline cells .	250	264	211	406	68
Transitional cells . .	137	240	194	56	—
X-cells	114	168	130	238	34
Polynuclear eosinophiles	22	96	—	42	303

[1] Only 100 leucocytes counted on this date.

Notes on blood of dog G. May 30th.—One megaloblast seen, and well-marked polychromatophilic degeneration. Macrocytes and microcytes numerous.

June 4th.—Four normoblasts seen, but no megaloblasts. Polychromatophilic degeneration, macrocytes and microcytes present.

June 11th.—Three megaloblasts, but no normoblasts seen. Well-marked polychromatophilic degeneration, macrocytes, microcytes, and poikilocytes present.

June 22nd.—Three normoblasts seen, otherwise the blood as before.

August 15th.—Fifteen normoblasts seen, otherwise the blood as before.

Animal killed ten weeks from day of operation. There was no evidence of rickets, and the animal was perfectly healthy. All the viscera were found to be normal, except the thymus gland, which weighed 9·58 grms. There were three definite areas of scar tissue in the parietal peritoneum where the "grafted" thymus gland had probably been attached, but there was no other evidence of any of the gland tissue in the abdomen.

Dog A.—*Small collie pup, weight* 1750 *grms. Intra-peritoneal graft of thymus gland (weight* 2·5 *grms.) from black pup of same litter. Operation October* 25*th,* 1903.

	Oct. 25th.	Nov. 11th.	Nov. 17th.	Dec. 12th.	Dec. 21st.
Red cells	?	3,484,375	4,709,355	3,743,750	?
Hæmoglobin	82%	70%	90%	60%	60%
Colour index	?	1	1	0·8	?
Leucocytes	30,400	27,940	4140	5980	6200
Differential count	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Polynuclear neutrophiles	60	68·2	51·8	31	46·2
Small lymphocytes	21·6	8·4	19·6	41·2	26·8
Large ,,	9	8·2	6	10·4	14
Large hyaline cells	3·4	9·6	5·2	5·2	4·4
Polynuclear eosinophiles	0·6	1·2	14·4	10·6	0·4
Transitional cells	2·4	1·8	2·4	1	7
X-cells	3	2·6	0·6	0·6	1·2
	Per c. mm.	Per c. mm.	Per c. mm.	Per c. mm.	Per c. mm.
Polynuclear neutrophiles	18,240	19,096	2149	1860	2864
Small lymphocytes	6566	2352	813	2472	1661
Large ,,	2736	2296	249	624	868
Large hyaline cells	1033	2688	216	312	273
Polynuclear eosinophiles	182	504	598	636	25
Transitional cells	729	504	100	60	434
X-cells	912	728	25	36	74

Notes on blood of dog A. October 25th.—Well-marked polychromatophilic degeneration; a few macrocytes and microcytes seen and slight poikilocytosis. 23 normoblasts and 1 megaloblast seen while counting 500 leucocytes.

November 11th.—29 normoblasts and 1 megaloblast seen while counting 500 leucocytes, otherwise blood as above.

November 17th.—113 normoblasts and 19 megaloblasts seen while counting 500 leucocytes; otherwise as above.

December 12th.—47 normoblasts; otherwise as above.

December 21st.—5 normoblasts; otherwise as above.

The blood from the pup used for grafting contained 6400 leucocytes per c.mm., and no nucleated red cells were seen, whereas the blood of the grafted pup, as above mentioned, contained 30,400 leucocytes per c.mm., and the red cells showed marked degenerative change, with numerous nucleated cells. The animal, though looking in excellent health, was therefore already showing considerable blood changes and might be very sensitive to any interference, such as an abdominal operation and an intra-peritoneal grafting of lymphoid tissue.

This puppy, a fortnight before it was killed, was a typical example of a rickety animal. It was killed two months from date of operation.

Post-mortem examination.—The skull was large and square. Frontal and lateral bosses were well marked, and craniotabes was most obvious. There was an extensive antero-posterior curvature of the spinal column. The legs were bent and bowed. All the epiphyses were very much enlarged. The abdomen was protuberant. The spleen and liver extended for some distance below the costal edge. There was hypertrophy of the glandular tissue throughout the body, especially of the mesenteric glands. The tonsils were not enlarged and neither were the tongue papillæ. The thymus gland was enormous and weighed 20·65 grms. (normal weight would appear to be about 2·3 grms.). The usual thick fluid was found in the interior of the gland. The spleen weighed 12 grms. instead of 6 grms., which is about the normal weight. The liver, pancreas, and other glands were enlarged. The intestines were normal. The thyroid gland, however, was not enlarged. The bone marrow from the shaft of the long bones was of a pale red colour.

Microscopical examination.—The chief points to be noted are:

(1) The animal died with many changes such as we find in lymphatism.

(2) There was well-marked evidence of rickets.

(3) The thyroid gland appeared to be normal.

(4) The thymus gland was hypertrophied.

(5) There was no evidence of hepatic cirrhosis and no evidence of the formation of red blood corpuscles in the liver.

(6) There was no evidence of cirrhosis of the spleen. The glomeruli were obvious to the naked eye. Large hæmorrhages were scattered throughout the organ, but there was no evidence of hæmolysis having occurred. There were no eosinophile cells to be seen, and no true giant cells. A few normoblasts could be observed in every section.

Dog H.—*Control pup, same litter as dog G, weight* 950 *grms. Abdominal section. Forceps introduced and moved about in belly cavity. No thymus grafted. Operation, May* 31*st.*

	Before operation.	After operation.	
	May 30th.	June 11th.	Aug. 15th.
Leucocytes	12,360	10,040	8560

	Before operation	After operation.		Before operation	After operation.	
Differential count	May 30. Per cent.	June 11. Per cent.	Aug. 15. Per cent.	May 30. Per c. mm.	June 11. Per c. mm.	Aug. 15. Per c. mm.
Polynuclear neutrophiles	52·8	57·8	52·4	6526	5780	4485
Small lymphocytes . .	36·4	26·8	25·6	4500	2680	2191
Large „ . .	3	10·4	8·2	371	1040	702
Large hyaline cells . .	4	2·2	2·4	494	220	205
Transitional leucocytes .	—	·6	·6	—	60	51
X-cells	1·6	1	·6	198	100	51
Polynuclear eosinophiles.	2·2	1·2	10·2	272	120	873

Notes on blood of dog H. May 30th.—One megaloblast and two normoblasts seen. A few macrocytes, microcytes, and poikilocytes present.

June 11th.—Four normoblasts but no megaloblasts seen. Macrocytes, microcytes, poikilocytes, and polychromatophilic degeneration present.

August 15th.—Seventy-eight normoblasts and twelve megaloblasts seen. Many macrocytes, microcytes, and poikilocytes present. Polychromatophilic degeneration.

Post-mortem examination.—This animal was killed ten weeks from date of operation. There was well-marked evidence of rickets in all the bones. The abdomen was large and protuberant. The lymphatic glands throughout the body were enlarged, but only slightly. There was no enlargement of the tonsils or of the papillæ of the tongue. The thymus gland was very large, and weighed 17·8 grms. The usual fluid was present in the interior of the gland. The thyroid gland was not hypertrophied. The spleen weighed 11·5 grms., a little more than twice the normal weight. Peyer's patches and the solitary follicles were hypertrophied. The bone-marrow obtained from the shaft of the various long bones was of a deep red colour.

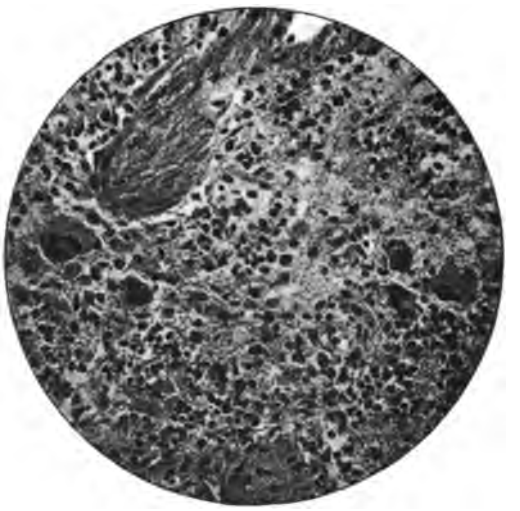
Microscopical examination of certain viscera.

Liver.—There was no evidence of cirrhosis, and we did not observe any evidence of red blood cell formation in this organ. There was no free iron reaction.

Spleen.—Glomeruli extremely distinct and prominent, both to the naked eye and on microscopical examination. Early fibrosis appeared to have commenced, and the endothelial cell proliferation was very marked. Enormous numbers of giant cells were seen (Fig. 45), many of which resembled the large type of "lymphadenoid" cells. We did not observe any pigment in any of these cells, although there was marked evidence of hæmolysis in the spleen, and we did not see any red blood corpuscles in these cells or any positive evidence of phagocytosis. In most of the giant cells the nuclei were arranged in the form of a ring about the centre of the cell. In some areas of the section the endothelial cells gave the impression that some were fusing together to form these giant cells. Numerous nucleated red blood corpuscles were seen in the section of the spleen.

Bone-marrow.—The giant cells were very numerous (Fig. 46); this was especially obvious when the sections of the bone-marrow

FIG. 45.



Spleen of dog. Section stained by Leishman's method. Numerous giant cells are shown in the section. The absence of granular material around these was notable as contrasted with its presence in the bone-marrow. [*A, obj.; B, eye-piece.*]

FIG. 46.

Section of bone-marrow from shaft of femur of dog. Stained by Leishman's method. Numerous multinucleated cells occur in the section; around each there is a finely granular substance. The giant cells are considerably more numerous than in the marrow of a healthy puppy of the same age. [*A, obj.; B, eye-piece.*]

were compared with sections of the marrow obtained from normal dogs. Many of these cells resembled the cells in the spleen; the nuclei of some giant cells were indistinct and appeared to have shrunk. Almost every cell stained by Leishman's method showed a fine granular marking around the circumference of the cell. This is constant both in the giant cells of animals and human beings. Neutrophilic and eosinophilic myelocytes were very numerous, far more than we have ever seen in the bone-marrow of normal puppies. Eosinophilic cells with a "transitional" nucleus were also present. Small and large non-granular mononuclear cells appeared to be very numerous; nucleated red blood corpuscles, both megaloblasts and normoblasts, were abundant.

Thymus gland.—The gland tissue was perfectly normal, but, contrary to what is usually found in the thymus gland of children and young animals, eosinophiles were extremely scarce.

In both dog A and dog H (control animal) we found well-marked evidences of rickets associated with the condition known as lymphatism. In the control animal (Dog H) there were also present severe changes both in the spleen and bone-marrow quite apart from lymphatism or rickets, and there was also evidence of hæmolysis. It is probable that helminthiasis may have been the cause of the eosinophilia both in the blood and bone-marrow, but we have also to account for the numerous giant cells in the spleen, far in excess of what we usually find in the spleen of young animals, and also for the hæmolysis. There was no positive evidence that the giant cells were in any way connected with the deposit of iron in the spleen, or otherwise the hæmolysis might be the cause of the presence of these cells in such large numbers.

It is of great interest to find that a dog used for the experiments and a control dog both developed such marked rickets, and in each instance there was hypertrophy of the lymphoid tissue throughout the body, namely, lymphatism. The thymus gland in each animal was greatly enlarged, but we did not observe any dyspnœa at any time and both animals withstood the effect of chloroform remarkably well, a fact which is of great interest when we consider the connection between lymphatism in children and sudden death. In both animals the red cells showed important changes, which have already been referred to, but we would especially notice that although there were such

marked alterations in the blood and blood-forming organs, yet we failed to observe the presence of any variety of myelocyte in the blood, whereas in the case of children with severe blood changes myelocytes are very common. We mention this fact because, although we have examined the blood of a very large number of both young and adult animals, we have never seen any variety of myelocyte in the peripheral blood.

December 20th, 1904.

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24. *The chemical examination of the gastric contents, with an accurate clinical method of determining the active hydrochloric acid present.*

By W. H. WILLCOX, M.D., M.R.C.P., B.Sc., F.I.C., Lecturer on Pathological Chemistry at St. Mary's Hospital.

THE attention which is being paid at present to the surgical aspect of diseases of the stomach is a sufficient excuse for the title of this paper.

During the last two years great strides have been made in the operative treatment of various gastric complaints, and there is no doubt that further advances will be made in this direction in the immediate future.

It is impossible, for example, to exaggerate the importance of an early diagnosis in cases of gastric carcinoma. The diagnosis is usually deferred until a definite mass can be felt. An operation is now performed, but too often other structures are found to be secondarily involved, so that the surgeon must perforce be content with the palliative operation of gastro-enterostomy, when an earlier diagnosis might have enabled the entire diseased part to be successfully extirpated.

For an early diagnosis to be made it will, I think, be generally agreed that a careful chemical examination of the gastric contents is of the utmost importance. It is most essential that the methods employed in this analysis should be of rigid scientific accuracy and also of clinical application. Approximate methods of analysis are of no value if fine distinctions are to be drawn

from the results. The analyses must be of absolute accuracy if advances in the early diagnosis of disease are to be made.

I. *The gastric contents.*

The vomit may be used for analysis if obtainable. Usually however it is better that the patient be given a test meal, and the gastric contents be drawn off subsequently. The patient should be kept on a restricted and light diet for a day or two before the test meal is given.

The test meal may consist of a pint of weak tea with about one ounce of milk and sugar to taste, or else a pint of thin arrowroot or other carbohydrate food, made with water and about two ounces of milk, sugar being added as required. With the liquid a round of thin buttered toast should be taken.

Test meals such as the above act as an efficient stimulus to the gastric secretion, and at the same time they render the subsequent analysis of the gastric contents easy. If test meals contain eggs, meat, large quantities of milk, etc., then the excess of proteid present combines with all the hydrochloric acid secreted and prevents the demonstration of free hydrochloric acid solution in the normal stomach. Hydrochloric acid, combined with proteid, cannot be demonstrated qualitatively; its detection depends on a careful quantitative analysis, which is described below.

The test meal should be given in the morning, before any other food is taken, and the gastric contents should be drawn off in an hour and a half. In removing the gastric contents, it is important that there should be no dilution with water, or the results of the analysis will be affected. A long soft tube should be passed into the stomach with an external portion longer than that in the alimentary canal. The air should be withdrawn from the tube by a syringe, and the syphon action started, when the fluid will gently flow out on the removal of the syringe.

II. *General examination of the gastric contents.*

The deposit from a portion is carefully examined microscopically. Starch granules, yeast cells, bacteria (sarcinæ, etc.),

striped muscle-fibres, epithelial cells may be found, the latter often being very numerous in gastric carcinoma.

The gastric contents are examined as to their general appearance—*e. g.* acidity to litmus, smell, consistency, the presence of slimy mucus, etc. They are filtered, and the filtrate is used for the subsequent examination. The clear filtrate should be tested qualitatively for the following: free hydrochloric acid and lactic acid (see below), albumen, mucin, albumose, peptose, dextrin, sugar, all of which are commonly present. Bile-pigments and blood should be tested for if the contents are coloured.

III. *Special chemical examination.*

(*a*) *Total acidity.*—This is determined by titration with decinormal alkali. Twenty c.c. of the filtered contents are measured by pipette, diluted with about an equal quantity of water, and the alkali is run in from a burette. Phenol-phthalein and litmus are the indicators in common use. They indicate the total free inorganic and organic acid, and also the HCl combined with proteid and other organic bases. Phenol-phthalein is the more convenient, since the titration may be done in the cold, litmus requiring a boiling temperature in order to remove carbonic acid. It should be remembered, however, that phenol-phthalein differs from litmus in the presence of alkaline carbonates; thus, bicarbonates are neutral to phenol-phthalein while alkaline to litmus, so that the results are slightly higher with phenol-phthalein than with litmus if carbonates are present.

Decinormal caustic soda is most commonly used as the alkali. It should be made by dissolving pure caustic soda (from alcoholic solution) in air-free water, and the solution should be so kept that it may not absorb carbonic acid from the atmosphere.

Decinormal barium hydrate solution is still more accurate, provided that dissolved carbonic acid is removed from the gastric contents before the titration by passing a current of air through the warmed liquid. Here phenol-phthalein gives a very accurate result as indicator, which is identical with that if litmus be used. The total acidity is usually expressed as percentage of acid calculated as hydrochloric acid.

(β) *Determination of the physiologically active hydrochloric acid.*—The secretion of HCl is one of the most important and

characteristic features of the stomach, and from the presence and amount of this substance in the gastric contents the most valuable aids to diagnosis are obtained.

Now, in the gastric contents hydrochloric acid may exist in three forms:

(1) Free HCl . . . . . } physiologically active.
(2) Combined HCl (α) with proteids and nitrogenous organic bases } physiologically active.
(β) with inorganic bases, as sodium chloride.

It is obvious that what is necessary to be known is the amount of "physiologically active" HCl. Many misconceptions have arisen from the use of the terms "free" and "combined" as applied to hydrochloric acid. It is often thought that the presence of free HCl is of more importance than that of the combined acid. This is not necessarily the case. Hydrochloric acid which is combined with proteid and nitrogenous organic bases is HCl which a short time before was free, but which has already commenced its important duties in the process of digestion; it is therefore of quite equal importance with free HCl. The relative amounts of free and combined HCl depend solely on the quantity of proteids and organic bases present. Of course the HCl combined with inorganic bases need not be considered. It is introduced into the stomach in the combined state as inorganic chlorides—*e. g.* sodium chloride.

It is hence of the utmost importance that the physiologically active HCl should be determined by an absolutely accurate method, and one which can be quickly and simply performed —*i. e.* be of clinical application. Also the HCl should be "directly" estimated, and not calculated indirectly from a titration of the acid present, since much greater accuracy results from a direct estimation of the chlorides present.

Few of the methods described yield an accurate determination of the active hydrochloric acid, and many are very complicated. The method I have used for upwards of a year, and which is a simple application of Volhard's determination of chlorides, is one which can be quickly performed with simple apparatus, and it is of the greatest accuracy, as I have repeatedly demonstrated.

The following is a description of the process: Two equal volumes of the filtered gastric contents (20 c.c.) are taken.

(*a*) One portion is diluted with about 40 c.c. distilled water, 10 c.c. pure nitric acid added, and about 5 c.c. of solution of iron alum. A measured excess (30 c.c.) of decinormal silver nitrate solution is added. Decinormal ammonium sulphocyanide solution is run in from a burette until a permanent reddish-brown tint just results. The difference between the quantity of silver nitrate solution added and the ammonium sulphocyanide solution used gives the amount of total chlorides present as decinormal hydrochloric acid. (*Note.*—If the amount of gastric contents is limited, the 20 c.c. may first have the total acidity determined by titration with $\frac{N}{10}$ caustic soda solution, phenol-phthalein being used as the indicator, and this liquid is then used for the total chlorides estimation exactly as described above.)

(*b*) The other portion of the gastric contents (20 c.c.) is placed in a porcelain evaporating basin (four and a half inches in diameter) and evaporated to dryness on the water bath; the solid residue is heated for about an hour on the water bath and the dish is then placed on a piece of wire gauze and heated with a small Bunsen flame, the flame not coming in actual contact with the basin. The heating is continued for about ten minutes until the residue is well charred. The dish is cooled, about 60 c.c. of water and the pure nitric acid are added, the contents being well stirred with a glass rod. The titration is performed exactly as in (*a*), and the quantity of chlorides present is given in terms of decinormal hydrochloric acid. The difference between the chlorides present in (*a*) and (*b*) expresses with great accuracy the amount of the physiologically active HCl.

Proof of accuracy of method.

I have repeatedly tested this and have invariably found the results extremely accurate.

Example.—A solution of HCl of known strength was made up, 1 per cent. of commercial peptone being added. The above method gave:

Amount of HCl (active) found = ·984 per cent.
„ „ actually added = ·989 „
Experimental error . . . = ·005 „

Similar accuracy is obtained with smaller percentages of HCl.

Notes on the process.

The effect of igniting the dried residue of gastric contents is to drive off the free HCl, and also to decompose the organic bases which have been combined with HCl, causing the latter to be also volatilised; the loss in chlorides therefore represents the "active" hydrochloric acid.

It is important that the dish should not be heated over a free flame, or else inorganic chlorides may be volatilised.

The presence of the black particles of carbon due to the charring does not in the least interfere with the accuracy of the titration, since the white precipitate of silver chloride and silver sulphocyanide forms an effectual contrast to this, and the first appearance of the red-brown tint can be immediately seen. It is not necessary to filter off the charred particles, as this introduces errors and makes the process more complicated.

Experiments related to the HCl determination.

(1) If peptone or albumen are added in excess to hydrochloric acid of a strength equivalent to that in gastric juice, and the solution is evaporated to dryness and heated on a water bath for several hours, there is no loss of HCl. Hence a temperature greater than that of the water bath, *i.e.* ignition, is necessary in order to drive off the HCl combined with organic bases.

(2) If HCl of strength as in the preceding experiment is mixed with dextrose or dextrin and evaporated to dryness and heated on a water bath for two hours, there is only a partial loss (about one-third) of the hydrochloric acid. This proves that in the gastric contents prolonged heating on the water bath only partially drives off the free HCl.

Review of methods described for estimating hydrochloric acid in gastric contents.

(1) Sjoqvist described a method of estimating "free HCl" by evaporation to dryness with barium carbonate, and igniting and estimating the barium chloride formed. The HCl combined with proteid is not estimated.

(2) Leo's method: Total acidity is determined by titration

with $\frac{N}{10}$ NaOH, using phenol-phthalein as indicator, a correction being made for acid phosphates. Here the HCl is not directly estimated and organic acids cause errors.

(3) Toepfer's method: Titration with $\frac{N}{10}$ caustic soda, using several indicators—*e. g.* (α) phenol-phthalein for total acid; (β) alizarin for free HCl and organic acid; (γ) di-methyl amido azo-benzene for free HCl. Here the HCl is not directly estimated, also the indicators only give approximate results; they do not act quite as stated—*e. g.* titration (γ) might include some organic acid (see below).

(4) Shufflebotham ('Lancet,' September, 1900) in an able paper called attention to the importance of active hydrochloric acid, and rightly pointed out that free HCl is more often absent than present in the gastric contents of pathological cases. He gave a method of estimating the acids which is not of great accuracy: (α) The total acidity was estimated by titration with $\frac{N}{10}$ caustic soda, phenol-phthalein being the indicator; (β) organic acids were estimated by extraction with ether. This extraction takes about twenty-four hours and may then be incomplete to the extent of 10 per cent.

(5) Ham and Macleod ('Lancet,' August, 1903) gave a most interesting method of determining free HCl depending on the hydrolysis of cane-sugar by gastric juice. The estimation takes twenty-four hours, and requires a calculation by logarithms from a somewhat complicated formula. The polarimeter is used in the determination. The method is valuable for determining free HCl, but does not estimate the HCl combined with proteid, which is usually the much more important factor owing to the very frequent absence of free HCl.

(6) Dr. B. Dawson (Allchin's 'System of Medicine') gives a method of determining free HCl and organic acid. This method is not accurate, since in the determination it is assumed that all the free HCl is driven off by heating on the water bath for one hour, which I have shown above is not the case. Also, the HCl combined with proteid is not estimated in this method.

Qualitative tests for free hydrochloric acid.

I have made numerous experiments in order to determine the most accurate method of detecting free HCl. There is no doubt that Gunzberg's test is the most reliable. It is most important that the reagent should be freshly made up for each test. If the solution is made in bulk, it loses its delicacy in a few hours and becomes useless for accurate work. The best way of applying the test is to keep the phloroglucin and vanillin in bottles, to the corks of which are attached little scoops which will measure about four grains of the former and two grains of the latter. These quantities are placed in a dry porcelain evaporating dish with 1 c.c. of alcohol (pure methylated spirit does quite well), and then about 2 c.c. of the filtered gastric contents are added. The dish is heated on the water bath till its contents are nearly dry. A brilliant scarlet-red colour indicates free HCl; a yellow colour is negative.

I have found that 1 part in 100,000 of HCl is clearly demonstrated by this test. Organic acids do not give the test, even if present in great quantity—*e. g.* to the extent of 1 per cent. or more. At the same time, they do not interfere with the positive reaction if free HCl is present. Carbohydrates and fats do not interfere sensibly with the delicacy of the test.

The test does not indicate at all the presence of HCl combined with proteid or organic bases, only a yellow residue resulting, no pink or red colour being formed. Of course if there is free HCl present, as well as HCl combined with proteid, then a positive reaction results, a red colour being formed.

Dimethyl amido azobenzene in alcoholic solution has been much used as a test for free hydrochloric acid. It gives a pink-red colour with free HCl in a solution as weak as 1 in 100,000. I have found, however, that the characteristic change of colour is given by lactic acid in strength as weak as 1 in 10,000, and by acetic acid in strength as weak as 1 in 2000. Hence, this reagent is not nearly so reliable since organic acids may give a reaction for free HCl when it is not present. On several occasions I have found that the gastric contents gave a positive reaction with this reagent, when subsequent investigation showed that no free HCl, but organic acid, was present. The reagent does not react to HCl combined with proteid.

Tropæolin OO and Congo red have been recommended as tests for free HCl. I have found them to be less delicate than the two preceding reagents, and that they react to organic acids.

Testing for organic acids.

A qualitative test should be made, a weak solution of Uffleman's reagent being added to the filtered gastric contents. The development of a distinct yellow colour indicates lactic acid. Acetic and butyric acids do not produce the marked yellow colour which is given by lactic acid, even in as weak amount as 1 in 5000.

The quantity of organic acids is given with sufficient accuracy for practical purposes by the difference between the total acidity and the amount of "active" hydrochloric acid as estimated by the method described in detail above. Of course the organic acids may be directly determined by ether extraction (Shufflebotham's method). I do not find this usually necessary.

Conclusions from the results of a large number of analyses of gastric contents.

In gastric and duodenal ulcer the acidity is usually high. Free HCl is generally present. The amount of active hydrochloric acid is high; it may be from ·1 to ·3 per cent., and is usually over ·2 per cent. Organic acids are absent or present only in small amounts. Peptone and other proteids are present in only small amounts, or are absent.

In temporary dyspepsia, e. g. vomiting from migraine, free HCl may or may not be present (depending on the food taken previously). The amount of active HCl is usually from ·1 to ·2 per cent., *i. e.* nearly normal in amount. Albumose, peptone, and other proteids are often present, organic acids only in small amount.

In carcinoma of the stomach I have found that the condition of the gastric contents varies very markedly with the position of the growth, so much so that the analysis enables one to say whether the cardiac or pyloric portion of the stomach is affected.

In growths of the cardiac portion of the stomach the total acidity is very small, often *nil.* Free HCl is always absent. Active HCl is frequently absent or present only in traces, *e. g.*

usually under ·04 per cent. Organic acids are generally present, albumose and peptone, mucin and albumen present in traces only.

In growths of the pyloric portion of the stomach, the cardiac portion being free. The acidity is fairly high—nearly up to the normal amount sometimes, but usually about one half the normal strength. Free HCl is scarcely ever present. Active HCl may be present in considerable amount, usually from ·05 per cent. to ·1 per cent.; it is thus decidedly reduced in amount; it scarcely ever exceeds ·1 per cent. Peptone, albumose, mucin, and albumen are present in large amounts as a rule. Also a considerable amount of organic acid is present. The above conclusions are based on careful analyses in upwards of fifty cases.

February 7th, 1905.

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25. *Carcinoma of the cardiac orifice of the stomach, involving the œsophagus.*

By John Fawcett.

Description of Specimen.—A portion of an œsophagus and stomach laid open to show a large mass of growth around the cardia extending downwards into the stomach, and upwards into the œsophagus. The œsophagus presents several portions of growth detached from the main mass. The highest one, at a distance of four and a half inches from the cardiac orifice, is a rounded polypoid outgrowth with a short, flattened pedicle, and its surface is studded with delicate villous projections. An inch below this nodule is a similar elongated deposit of growth, and immediately beneath it is another flattened projection directly continuous with the main mass of growth in the stomach. Along the line of junction of œsophagus and stomach are several smaller polypoid growths, also presenting delicate villi on their surfaces. In the stomach the growth extends downwards in a fan-shaped manner for a distance of 20 cm. and measures 11·25 cm. from side to side. The walls of the organ are infiltrated by the growth, which projects into the cavity of the stomach for a depth of an inch in some places. The inner surface of it is ulcerated, and only in parts of it in this region

can any villous processes be seen. The growth, as a whole, appears to involve chiefly the mucous and submucous coats, but on the posterior aspect of the organ it has spread through all the coats of this viscus.

The cardiac orifice is completely occluded by the growth. The lower four inches of the œsophagus are dilated.

Histologically the growth is a cylindrical-celled carcinoma.

I have brought this specimen before the notice of the Society with the object of drawing attention to two points in connection with carcinomatous growths involving the cardiac orifice of the stomach.

Drs. Perry and Shaw, in their paper in the 'Guy's Hospital Reports for 1891,' state that, in their opinion, primary malignant œsophageal growths with the exception of the sarcomata belong almost entirely to the class of squamous epitheliomata. They hold that the spheroidal-celled carcinomata, which have been described as originating in the lower end of the œsophagus, and extending to the cardiac orifice of the stomach, really arise in the stomach and not in the gullet. Their conclusion is based upon a microscopical examination of more than thirty cases of malignant disease from all parts of the œsophagus, of which every cancerous growth was an epithelioma. Dr. Fagge, in his text-book, arrives at exactly the opposite conclusion as to the place of origin of these growths, stating that "the 'Pathological Transactions' seem not to contain a single example of cancer beginning in the stomach at its œsophageal end; nor does the museum of Guy's Hospital show any specimen in which the lower end of the œsophagus is not also affected."

In this connection I thought it would be of interest to try and find out with what frequency the œsophagus was involved in growths affecting the cardiac extremity of the stomach, and Drs. Perry and Shaw's last paper in the 'Guy's Hospital Reports' for 1904 (vol. lviii) has given me an opportunity of investigating it.

Out of the 306 cases of malignant disease of the stomach upon which autopsies were performed and reports made between the years 1826 and 1900, there are 26 cases in which the cardiac orifice was involved. Of these one case was a sarcoma, and in another, although the growth was near the cardia, yet it did not appear to actually implicate the orifice. Thus 24

cases (or 7·8 per cent. nearly) remain for investigation, and of this number the œsophagus was invaded in 16 cases. Although, then, malignant disease in this region is rare as compared with the remainder of the stomach, yet the frequency with which the œsophagus is involved is striking, even if not quite so complete as that indicated by Dr. Fagge.

It is possible that this number might be augmented, in that only those cases are included in which it is definitely stated in the reports that the growth had involved the œsophagus. All these growths were undoubtedly primary in the stomach, but only three out of the 24 examples could be said to be limited to the cardiac region, for in the remainder the stomach wall was invaded for a considerable distance, 3–4 inches or more.

The second point which I wish to refer to is in connection with the histological structure of growths involving the cardiac orifice. Fourteen of the cases are available for examination. Of these nine are examples of the spheroidal-celled and five of the cylindrical-celled type.

In Drs. Perry and Shaw's paper in the 'Guy's Hospital Report' for 1891 they state that of the 50 cases of malignant disease of the stomach which they had examined "there is nothing special which renders it likely that a growth situated at any one part should have the histological structure of one rather than the other form of cancer," with the possible exception that in the mucous membrane around the œsophageal orifice they had "failed to find a limited growth of the cylindrical-celled type." This suggests that growths limited to the region of the cardia might be always of the spheroidal-celled type. Such limited growths are very rare. There are three in their original paper (1891), and in the later paper two more. Both of these latter are cylindrical-celled carcinomata, so that the conclusion is that the position of the growth forms no guide to its histological structure.

In the years 1901–1903 inclusive *post-mortem* examinations have been made at Guy's Hospital upon 41 cases of carcinoma of the stomach. Of these six involved the cardiac orifice, but only four cases could be classed as growths limited to the cardiac extremity, in that in two of the cases there was an infiltration of the whole organ. The œsophagus was invaded in one of the four cases. There were two cases of cylindrical-celled

cancer, one spheroidal-celled, and the other is described as "scirrhus," no mention of the type of cells being made.

As regards the origin of the growths involving the stomach and the œsophagus, I think there can be little doubt that Drs. Perry's and Shaw's conclusion is the correct one—viz., that such growths originate in the stomach and not in the œsophagus.

April 4th, 1905.

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26. *The etiology of carcinoma.*

By Keith W. Monsarrat.

In a paper read before the Royal Society 1891 (1) I described the morphological characters of an organism isolated from carcinomata. During the last four years these researches have been continued, but have been confined to one clinical type of carcinoma—that affecting the female breast. These further researches have provided material out of which I have been able to construct the life-history of the organism, and have also afforded evidence of interest and importance relating to the question whether the organism is etiologically connected with the disease.

The isolation of the organism.

All the material which has been used in the attempts to isolate the organism has consisted of specimens of unulcerated carcinoma mammæ removed by operation. These have been examined in the laboratory at periods varying from half an hour to four hours after removal, and with one exception I have been present at each operation, and have been personally responsible for the precautions taken to prevent contamination. These precautions I have described in a recent paper (2), so that I need not here refer to them in detail.

The specimens thus treated have been twelve in number. From seven of these I have isolated the organism I am about to describe, one was contaminated with *Staphylococcus epidermidis*

albus, the remaining four yielded no cultures. A large variety of nutrient media have been tried, but the positive results have been obtained with ordinary nutrient broth, in one case with glucose broth (4 per cent.) and glucose agar (1 per cent.) in the other six. In all cases the method of cultivation has been that of immersing small pieces of the growth in the fluid media, and rubbing pieces over the surface of the solid medium, or leaving small slices on the surface of the medium. All tubes have been incubated at 37° C., and all the positive results have been obtained under aerobic conditions.

The morphology and life cycle of the organism.

The organism is remarkably polymorphic. It exhibits two chief types, which differ to a marked degree (*a*) in morphology, (*b*) in behaviour in culture media, and (*c*) in the effects which they produce in the animal body. These two types I shall describe as Type A and Type C. I have been able to observe the changes which the organism undergoes in passing from one type to another, but not, hitherto, to determine exactly the conditions which govern and control these changes.

Type A is that form of the organism which is found in the primary cultures derived from the carcinomata; in one of the seven cases which I am here reporting Type C was associated with Type A in these primary cultures, but, with this exception, Type A alone was present in these cultures.

In the form of Type A the organism is spherical; its size varies from that of a minute spherical granule to a diameter of 2 μ to 3 μ.

In the fluid media it is seen partly suspended, but for the most part as a sediment; on the solid medium it occurred as a scanty greyish-white, very viscid and translucent streak. The viscosity is a marked characteristic. The amount of growth obtained has been very small in all cases; in no case was I able to obtain more than one generation of subcultures, and in most instances no subcultures at all developed.

The inoculation experiments also showed that the vitality of this type of the organism was of a very low order on the media employed.

In this form the organism is liable to be mistaken for a coccus;

the pronounced disparity in size of the different specimens is the chief peculiarity which distinguishes it from this class of organism.

In no case have I observed a development of this Type A into Type C *in vitro*. After injection into the animal body Type A may either (1) show no marked morphological change, or (2) exhibit changes in the course of which specimens develop of somewhat larger size than those in the culture, along with oval and club-shaped forms, or (3) pass on in development to what I shall now describe as Type C.

Type C is a spherical form, of a diameter varying from 5 μ to 10 μ. It possesses a capsule, a cell network, and one, a few, or many refractile granules in the interior. Romanowski's stain shows the presence of nuclear bodies, which may be single or multiple; as many as eight of these nuclear bodies have been observed within a single cell, each usually surrounded by a clear "halo," but this is not constant.

Type C multiplies readily on media, in particular on glucose-containing media, by budding. The details of this process, and the full description of the morphology of this type have been described by me in a recent paper (3).

Type C has been found in the course of my observations (*a*) in the lesions in animals which have followed inoculation with Type A, and (*b*) in one case (excluding those reported in 1899) associated with Type A in the primary cultures obtained from the carcinomata.

The development of Type C from Type A has been followed in a considerable number of animals inoculated with the latter. In all these animals with one exception the number of organisms which showed the characteristic structure of Type C was small, and none showed the budding process peculiar to this type. In the one exception the number of specimens of Type C was large, and they showed active budding.

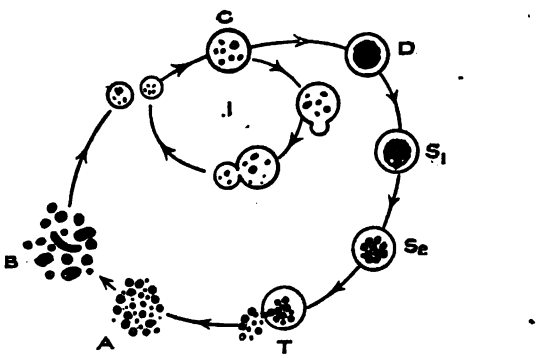
From these lesions which resulted from the inoculation of Type A either no cultures at all were recovered, or cultures of Type A similar to that injected. The exceptional case just mentioned was also exceptional in this respect, in that cultures of Type C were recovered from the lesions.

It has already been stated that Type A grew on media to a very slight degree only, and this difficulty of cultivation was further shown in that many of the animals the lesions in which

showed microscopically the presence of Type A yielded no cultures. On the other hand, by direct inoculation from animal to animal by breaking up the nodules which had been experimentally produced, in normal saline, and injecting the material thus obtained, I was able to produce a series of lesions in which the organism showed no diminution of activity.

From these observations it follows that the organism in the form of Type A must be described as a facultative parasite, whereas in the form of Type C, which grows luxuriantly on different kinds of media and also shows a capacity for develop-

FIG. 47.



Scheme of the life-history of the organism: I. Vegetative cycle. A. Type A, the form in which the organism occurs in primary cultures from carcinomata mammæ (facultative parasite). B. Intermediate (? involution) forms of A. C. The vegetative type (facultative saphrophyte). D. Form of C with interior taking dense chromatin stain. S_1 S_2. Stages in the process of sporulation. T. Sporulation process showing extrusion. All specimens stained wet with methyl violet.

ing in the animal body, it must be described as a facultative saprophyte.

By combining the observations it is possible to construct a scheme of the life-history of the organism as above.

In addition to the method of reproduction by budding which Type C exhibits, I have ascertained that this form of the organism proceeds to the development of a sporulating process. In spite of a large number of observations designed to discover the occurrence of this process *in vitro* I have not been able to produce it under these circumstances. The process was observed in animals which had been inoculated with cultures of the Type C form; it was also discovered in the one case of which I have

made mention above in which the primary cultures from the carcinoma showed organisms of both types; in these cultures a few specimens of the C type showed the sporulation process in a very distinct manner.

The process consists in the separation of the interior protoplasm of the cell into small spherical bodies and the extrusion of these through a dehiscence in the capsule, which is denser than that of the ordinary specimen of Type C. These small spherical bodies when extruded give the staining reactions and present the same general appearances as the organisms which have been described as Type A.

To recapitulate the characters of the two main types. Type A is that form which is to be found in primary cultures from the carcinomata; in all the cases here recorded, with one exception, this was the only type present in these cultures; in the one exception it was associated with Type C, the latter being in part in a sporulating condition. Type A grows on ordinary media either not at all or to a very scanty extent only; after injection into animals it usually remains unchanged, but may show certain morphological alterations in the course of which a few specimens similar in all respects to Type C are produced. In a single animal the specimens of Type C were present in large numbers in the lesions following inoculation with Type A.

Type C was cultivated from the animal just mentioned, and in one case direct from a carcinoma. In this form the organism grows abundantly on ordinary media. On injection into animals it may remain unchanged or may develop a process of sporulation which results in the production of organisms which resemble Type A; this sporulation process was also observed in the single case in which Type C was found in the primary cultures from a carcinoma.

The appearances presented by the organism after inoculation into animals.

Both forms of the organism are readily demonstrated in the tissues after inoculation, by Gram's method. Both give rise to a certain degree of proliferation on the part of certain of the cells of the tissues with which they are brought in contact, but Type A presents an important difference from Type C in regard to its

relation to these proliferating cells. Whereas Type C is not seen within cells, but between them and in interstices in connective tissue, Type A is found characteristically as an intra-cellular parasite, usually extra-nuclear, occasionally intra-nuclear. Type A is demonstrable as an intra-cellular parasite by Gram's method. Usually single specimens were seen within the cells, but from two to five have been observed in a single cell. Single specimens lie in a vacuole in the cell, which appears as a clear space or "halo" around the organism. If more than one specimen is present in a cell, each may lie in a separate vacuole, or the vacuole may be common. The organisms within the cells show the same marked variations in size as are to be seen in the cultures *in vitro*. They were seen within endothelial (peritoneal) and epithelial cells and in these alone. They were not numerous in any of the lesions, from one to three being usually visible in each microscopic field (Leitz $\frac{1}{12}$ in. objective; eyepiece IV). The organism *in the form of Type A* is therefore capable of infecting and entering epithelial and endothelial cells.

The lesions produced in animals by inoculation of the organism.

Before describing the lesions which are produced by the inoculation of the organism in the form of Type A, which description is the second of the two chief objects of this paper, I shall first shortly refer to the effects which are produced by inoculation of the actively vegetating Type C. These I described at length in the paper (4) to which reference has been made above, and the observations there recorded have been confirmed by later experiments, particularly by the examination of lesions in animals at varying periods after injection. When a culture of this type is inoculated intra-peritoneally the early effect is the local stimulation of the endothelial cells of the peritoneum to proliferation, so that small nodules are formed composed of masses of these endothelial cells, with numbers of the organisms between them. The organism in this type does not show a capacity for entering and inhabiting the endothelial cells; it continues its active multiplication by budding, with the result that the new-formed endothelial cells become compressed, and the nodules are vacuolated. Ultimately these nodules consist of masses of the organism, with a network

of connective-tissue-like appearance around and between them. Analogous processes have been observed in other organs and tissues.

The effect which the organism produces when injected into the animal body in the form of Type A is of a quite different character.

The effects have been uniform with the exception of a certain number of negative results, which were apparently due to the rapid loss of vitality which this type displays *in vitro* in the media which I employed.

In stating that the results were uniform I do not intend to convey that the extent of the lesions produced has been equally great in all the animals used, but that the general character of the lesions was the same in the different animals.

A total of 23 guinea-pigs have been inoculated, and lesions were produced in 13 of these; 2 were inoculated subcutaneously without result; the rest were inoculated into the peritoneal cavity. Three dogs have been inoculated, 1 into the peritoneal cavity, 2 into the mammary gland; in all three cases lesions were produced. These numbers are, of course, exclusive of those animals which are still under observation. In illustration of the characters of the lesions, I shall describe those in two guinea-pigs and two dogs.

Guinea-pig 1.—Inoculated into the peritoneal cavity, killed twenty-four days later. Nodules were found in the peritoneum, the abdominal glands, the liver, the lungs, and the spleen.

The peritoneal nodules consisted of masses of large oval, spherical, and polygonal cells arranged in part in parallel columns but also in part in an alveolar manner, in groups in the interstices of a stroma. The masses of cell-growth were not defined at their margins, and at this situation the typical parenchyma cells were seen within perivascular lymphatic spaces; these cells could be definitely traced to have arisen by proliferation of the endothelium of the peritoneum.

The glands show areas which stand out when stained from the normal gland tissue and the differentiation can be seen with the naked eye. These areas are found to possess a structure which shows a definite resemblance to that of the peritoneal nodules both in the character of the cells and their arrangement.

The liver nodules are all situated in the portal canal regions;

they consist of oval and spherical cells arranged in columns and masses bordered by connective tissue. It is seen that these columns and masses have originated by proliferation of the epithelium of the small bile-ducts; they extend directly from these into the surrounding tissue in the portal canals and form masses of considerable size which separate and compress the hepatic lobules.

In the lung the nodules stand out as whitish patches of irregular shape; the majority can be traced to a connection with small bronchioles, and from the epithelium of these they have arisen; in one or two instances the new-formed cell masses can be seen infiltrating along the lumina of bronchioles, but for the most part the direction of growth has been into the surrounding tissue; the cells of this new-formed tissue are arranged in an alveolar manner. In all the nodules—peritoneal, glandular, hepatic, and pulmonary—organisms were demonstrated by Gram's method within the new-formed cells.

Guinea-pig 2.—Inoculated into the peritoneal cavity; killed thirty-seven days later. The nodules in the peritoneum consist of oval and polygonal cells with a large cell body and large spherical and oval nuclei. Lymphocytes are present throughout the nodule in fair numbers. The arrangement of the cells is similar to that described in guinea-pig 1. The mesenteric glands are occupied by masses of cell growth, which reproduce in the character of the cells and their arrangement the characteristics of the nodules in the peritoneum.

The liver nodules are numerous; the type of the cells composing these nodules and their arrangement are exactly similar to those of the peritoneal nodules. The new cell growth cannot, as in guinea-pig 1, be traced to the small bile-ducts, and its structure is different from that found in guinea-pig 1.

I have recently had the opportunity of examining sections of a peritoneal carcinoma in the human subject kindly placed at my disposal by Dr. A. S. Grünbaum, and I find that the structure of this shows a marked resemblance to that of the nodules I have described in these guinea-pigs.

Dog 1.—Killed forty-two days after intra-peritoneal inoculation. Nodules were seen with the naked eye in the omentum, mesenteric glands, liver, and spleen. The omental nodules consist of a parenchyma and a stroma. The parenchyma consists of branched columns of epithelium-like cells irregularly arranged.

They can be traced from the surface endothelium, where their arrangement is in masses, downwards to the deeper parts, where they lie in a dense stroma. The mesenteric glands appear to be infiltrated with new tissue, which can be seen with the naked eye. This is similar in structure to the omental nodules in regard to both the character and arrangement of the cells. Nodules in the liver are situated in relation to the portal canals, and between them the liver parenchyma is compressed; they consist of branching columns of cells and of fine tubules in a connective-tissue stroma; the cells composing the columns and tubules show characters which are identical with those of the epithelium of the bile-ducts, but there are appearances also which seem to connect these cells with the parenchyma of the liver lobules, and the exact histogenesis of the nodules is somewhat uncertain. The spleen is studded with nodules; the structure of these is somewhat indistinct, but their general characters resemble those of nodules in the peritoneum.

Dog 2.—Killed eighty-two days after inoculation into the mammary gland. A single nodule the size of a large hazel-nut was present in the mamma, and there were numerous nodules in the spleen. The mammary nodule was composed of cells with large body and spherical or oval nuclei, supported by a fine connective tissue; lymphocytes were scattered throughout. The large cells are arranged for the most part in parallel columns within the stroma interstices, but the arrangement cannot be said to be regular or to have assumed a definite type. The nodules in the spleen are fibro-cellular; they are not marked off from the splenic pulp by any fibrous boundary; the cells are arranged in groups within the connective-tissue stroma, but their histogenesis is uncertain. The stroma is denser than in the mammary nodule, and the nodule on the whole does not reproduce the characters of the latter, although it bears some resemblance to it.

These four examples illustrate the character of the new tissue formation which follows inoculation with the organism; in one animal alone were there nodules in the kidney; these consisted of groups of cells arranged in a distinctly alveolar manner in a fine stroma, and derived by proliferation from the epithelial cells of the renal tubules.

In all the lesions examined the characteristic organisms were

demonstrated as intra-cellular parasites; occasionally intra-cellular specimens were seen.

Summary of the inoculation results.

The organism showed a capacity for initiating active proliferation of endothelial and epithelial cells. The new-formed tissue resulting from this showed a parenchyma and a stroma, and at its edges a progressive growth without encapsulation. In neighbouring glands there was found in some instances a formation of new tissue whose structure resembled that of the primary nodules. The nodules in viscera appeared as a rule to arise from epithelium *in loco*, and showed a capacity for active growth and infiltration similar to that observed in the nodules arising from endothelium. In one instance at least new-formed tissue in the liver reproduced exactly the characters of nodules in peritoneum and mesenteric glands, and, assuming that the observation that it did not arise from cells *in loco* was correct, must be considered a true visceral metastasis.

Demonstration of the organism in human carcinoma.

Having found that the organism was demonstrated by Gram's method within the cells of the experimentally-produced nodules, the application of this method to carcinoma mammæ naturally followed.

My observations on this point have up to the present been few in number and relate to three cases only. In these three carcinomata Gram's method shows the presence within the parenchyma cells of bodies which give the same staining reaction and have the same general appearance as the parasites in the cells of the experimentally-produced nodules; in the latter they were few in number in most cases, and in the carcinomata also they were not numerous. In the nodules they have been described as occupying vacuoles in the cells outside the nucleus; in the carcinomata they occupy the same position; in both cases they were also seen within nuclei forms which presented the same appearances, but this was an exceptional occurrence.

Summary of researches.

(1) From a considerable proportion (58·3 per cent.) of specimens of carcinoma mammæ an organism presenting characteristic features was isolated.

(2) This organism presents a life-history in which two cycles were traced—the one a vegetative budding cycle, the other a sporulating cycle.

(3) The organism when injected into animals is capable of infecting and inhabiting endothelial and epithelial cells.

(4) The organism initiates in endothelium and epithelium a process of proliferation as a result of which masses of new-formed tissue are built up which consist of a parenchyma and a stroma, and grow and extend actively from their centres of origin.

(5) This new cell-mass formation may be associated with growth of a similar character in neighbouring glands, and some evidence was also provided that visceral metastasis occurs.

(6) Intra-cellular bodies are demonstrable in carcinoma mammæ, which present the same features as the intra-cellular parasites of the experimentally produced nodules.

(7) The evidence derived from these researches points to the conclusion that the organism described is an etiological factor in the morbid process known as carcinoma mammæ.

[The expenses of these researches were in part defrayed by a grant from the British Medical Association. A plate illustrating the paper will be found in the 'British Medical Journal,' Jan 23, 1904.]

REFERENCES.

1. 'Proc. Roy. Soc.,' December 14th, 1899.
2. 'Thompson-Yates and Johnston Laboratories Report,' vol. v, part i, 1903.
3. *Ibid.*
4. 'Proc. Roy. Soc.,' December 14th, 1899.

Report of a Committee of the Council of the Pathological Society upon the histology of the specimens exhibited by Mr. K. W. Monsarrat.

We have carefully examined the series of microscopic preparations submitted to us by Mr. Monsarrat, and except in regard to one of the specimens, we do not think that any

serious question arises as to the general character of the lesions experimentally produced by the author. We do not consider it necessary to report upon each of the preparations.

Taking, however, as the most crucial (since the initial) lesions the peritoneal nodules produced by intra-peritoneal injection of the micro-organism into guinea-pigs, these we do not regard as either sarcomatous or carcinomatous, but as belonging to the class of infective granulomata. The nodules consist of polymorphous endothelial or epithelioid cells without recognisable disposition, and of intermingled leucocytes, together with a certain number of multinuclear giant-cells; foci of necrosis, moreover, occur in the new-formed tissue with accompanying karyolysis.

In regard to the lesions artificially produced by the injection of the micro-organism into the mammary gland of the dog; these, again, we regard as inflammatory in nature, an abundance of polymorphonuclear leucocytes being present in places. No mammary tissue occurs in the sections, and nothing suggestive of carcinoma.

The most striking specimen of the whole we regard as the peritoneal nodule from the dog on which intra-peritoneal injection was carried out. In this animal the liver presents appearances accurately described by the author, but we do not regard these as other than indicating a cirrhosis in a somewhat acute form, the narrow cell-columns corresponding in all respects with the so-named new bile-ducts. In the greater part of the specimen there is perilobular inflammation of comparatively recent date, as evidenced by young connective tissue and polymorphonuclear leucocytes. This granulation tissue spreads into the lobules, tends to separate the hepatic cells from each other, and contains a number of branching columns of cells, arranged in parallel rows and bounding a potential lumen: these columns can in not a few instances be traced into direct continuity with the hepatic cells, and they are confined to the region of the periphery of the lobules.

The only specimen admitting of difference of interpretation is the peritoneal nodule of this same dog upon which the author states that intra-peritoneal injection of the micro-organism had been carried out.

The histological picture of this differs from that of the peri-

toneal nodules in the guinea-pigs, in that it is definitely alveolar. The nodule consists of cells of conspicuous size arranged in ramifying columns, as depicted by the author in the 'Brit. Med. Journ.,' Jan. 23rd, 1904.

The stroma between is of a loose connective kind, infiltrated in varying degrees with leucocytes, but everywhere sharply defined from the large cells of the columns, which in one or two spots show a disposition towards a nest or whorled arrangement. The committee is unable to confirm the view of the author that the cells in question arise in a proliferating endothelial investment.

Mitotic figures occur in no inconsiderable numbers, but the mode of preservation and the stain used do not allow of the determination whether heterotypical forms are present.

The author was good enough to place the paraffin block at the disposal of the committee, and Mr. Charles Walker undertook to re-examine the lesion for the above purpose, but no result could be arrived at, in consequence of the tissue not having been originally fixed for this particular object.

Having in view the fact that this specimen is the only one admitting of doubt out of the entire number furnished by the experiments,[1] the committee does not consider it proved that the micro-organism isolated by the author is the proper cause of a malignant new formation.[2]

(Signed) F. W. Andrewes,
W. Bulloch,
H. M. Fletcher,
A. G. R. Foulerton,
W. S. Lazarus-Barlow,
H. D. Rolleston,
S. G. Shattock,
G. F. Still,
C. P. White.

February, 1905.

[1] 21 guinea-pigs inoculated intra-peritoneally, 13 with a positive result; 1 dog inoculated intra-peritoneally; 2 dogs inoculated into the mammary gland.

[2] Mr. Foulerton agreed with the finding of the Committee in regard to all the specimens, including the section of the hepatic lesion from dog 1, but with regard to the omental nodule from the same dog he considered that the section submitted to the Committee as representing the nodule did not in every

27. *A prehistoric or predynastic Egyptian calculus.*

By S. G. Shattock.

De calculo vesicali in sepulchro prehistorico reperto.

Summarium.

Hic calculus, in museo collegii regii chirurgorum Anglici nunc conservatus, ab Elliot Smith repertus est in uno e sepulchris prehistoricis, prope Ægypti superioris vicum cui nomen hodie El Amrah.

Vicus ipse a situ Abydi antiquo haud procul abest.

Sepulchrum annis permultis abhinc despoliatum erat, sed vas lapideum relictum demonstrat sepulchrum multa sæcula exstitisse ante Menem, regem Ægyptiorum primum, qui anno circa 4800 ante Christum, ut computatur, regnavit.

way bear out the description given of the nodule by the author of the paper. The reference to the omental nodule in the author's paper is as follows:

"Nodules were seen with the naked eye in the omentum, mesenteric glands, liver, and spleen. The omental nodules consist of a parenchyma and a stroma. The parenchyma consists of branched columns of epithelium-like cells irregularly arranged (Fig. 1, 'British Medical Journal'). They can be traced from the surface endothelium, where their arrangement is in masses, downwards to the deeper parts, where they lie in a dense stroma."

Mr. Foulerton, observing that no part of the sections submitted show any sign of a "surface endothelium," was of opinion that they have every appearance of having been cut from a block prepared from the interior of a mass of new growth. Mr. Foulerton considered that the appearance of the section of the "omental nodule" indicated a pathological process totally different from that represented in any of the other sections submitted to the Committee, including the solitary other section of a lesion from the same animal, and consequently felt that, in view of the strong probability, as it appeared to him, that there might have been some error in the assortment of material, and that the section labelled "peritoneal nodule" had been so labelled in mistake, no positive expression of opinion should be given upon it.

Dr. Lazarus-Barlow differed from the other members of the Committee in regarding the hepatic lesion in the dog referred to as being possibly endotheliomatous, and like the peritoneal nodule in the same animal; he, however, would hesitate to ascribe these lesions themselves to the effects of the inoculated micro-organism.

De temporibus prehistoricis per explorationes a Flinders Petrie confectas cognovimus.

Haud barbara erat gens illa prehistorica; vasorum enim lapideorum, quæ per sæculum prehistoricum fingebantur, vis magna invenitur.

Quæritur utrum gens prehistorica Ægyptia ex Libyâ orta sit: hæc disputatio autem nihil nostra interest.

Nunc de calculo ipso dicamus. Hic inter ossa innominata pueri annorum circa sedecim repertus est. Ex substantiâ constat fulvâ et confertâ, cujus superficies fracta strias et radiales et concentricas ostendit.

Analysis chemica hanc substantiam ex acido urico constare probat.

Sectio microscopica, secundum artem petrologicam facta, calculum monstrat ex crystallis prægrandibus radialiter in columnis dispositis formatum esse. Fragmentis minutis liquori potassæ causticæ subjectis, acidum uricum dissolvitur et matrix translucida, ut solet, conspici potest.

Calculus tegmine crasso calcii phosphatis et ammonii magnesiique phosphatis circumdatur. Notandum est quod et chemice et in sectione microscopicâ calcii oxalas abest. [In talibus sectionibus e calculis factis facile distinguntur calcii oxalas, acidum uricum, et ammonii aut sodii uras.]

Apud Indos enim calculi plurimi ex calcii oxalate constant (70 per centum), quod ascribi debet imprimis alimentis quibus utuntur.

Per sæcula recentiora Ægyptiorum antiquorum alimenta ex oleribus præcipue constiterunt; ex tritico, hordeo, pisis atque lentibus.

Sepulchrorum autem exploratio probat Ægyptios prehistoricos venatores fuisse, lanceis venatoriis in sepulchris

quibusdam repertis, unâ cum pecudum imaginibus ex argillâ fictis.[1]

Demonstrare non potui, aut in calculi nucleo, aut in calcii phosphatis tegmine, capsulas adesse ovorum chitinosas Bilharziæ hæmatobii.

The calculus which forms the subject of the present communication was presented by Professor G. Elliot Smith to the Museum of the Royal College of Surgeons in 1901.

To the historical pathologist its great antiquity will invest it with a high interest, for it is itself the concrete and irrefragable evidence of the ancient existence of a disease not now obscure or beyond identification, but a disease which is at the present time one of the most widely spread and best known in Egypt.

Immensely more interesting would the specimen have proved were it possible to associate it with the Bilharziosis held by some to explain the present frequency of urinary calculus in Egypt. But this I am unable to do, for in spite of the most scrupulous manipulative care and the expenditure of an indefinite amount of time, my search for the chitinous capsules of the Bilharzia has been fruitless. Proof of the existence of Bilharziosis in the prehistoric or predynastic Egyptian age is at present, therefore, wanting.

Antedating as it does by at least three thousand years the Hebrew exodus (reign of Menepthah, 1320 B.C.), the specimen derives, moreover, a reflected interest from that event, itself, of such immeasurable consequence in the history of mankind. The question, indeed, has suggested itself to me whether the first of the biblical plagues might with any probability be referred to an epidemic of Bilharziosis arising from an infection of the Nile and the drinking of its waters,—whether the Bilharzial hæmaturia, so surprising and inexplicable as it would have been, might be taken as an interpretation of the biblical narrative. A reference to the narrative itself, however, will show the incongruities attaching to such an attempt.

I may first briefly notice what relates to the historical side

[1] 'El Amrah and Abydos, 1889–1901,' D. Randall MacIver, M.A., and A. C. Mace, with a chapter by F. Griffith, M.A., F.S.A. Special extra publication of the Egyptian Exploration Fund, 1902.

of the matter, and afterwards describe the structure, and note the chemical composition of the concretion.

The calculus was obtained under the following circumstances. In April, 1901, Professor G. Elliot Smith visited Upper Egypt in order to study the remains of the prehistoric people which were being excavated by Mr. David Randall MacIver and the late Mr. Anthony Wilkin.

The cemeteries investigated lie close to the cultivation on the table-land between two wide valleys which run down from the upper desert a short distance north of the village of El Amrah. The village itself is situated about six miles to the south of the ancient site of Abydos.[1] In one of the first graves dug out the donor observed the calculus lying amongst the pelvic bones. The grave was that of a boy, aged 16 years (numbered 2231 in Dr. MacIver's private notes). The tomb had been plundered at some ancient date, but a *stone* vase[2] remained to show that the grave was that of an individual of the predynastic period—*i. e.* of the middle or later-middle prehistoric period, some generations at least before the advent of Menes, the first dynastic king (about 4800 B.C.).

The knowledge of a predynastic or prehistoric age is of comparatively recent origin, and has grown out of the work carried on under the direction of Professor Flinders Petrie.

In the exploration of the cemeteries of Ballas[3] it became evident (said the authors of the work at that time) that part of the cemetery belonged to a people not Egyptian. This conclusion was deduced from the contracted position of the skeleton found uniformly in 3000 burials, from the small statuettes showing no trace of Egyptian style, and from the entire absence of objects known to be Egyptian. At Nagada the typical tombs are vertical pits, with the body laid on the floor; the pit in wealthy graves was roofed over with beams, etc., a system wholly foreign to the Egyptians. In place of the body being preserved intact and embalmed, the bodies were usually more or less cut up and destroyed; and, instead of being buried at full

[1] "A Prehistoric Cemetery at El Amrah; Preliminary Report of Excavations," by David Randall MacIver; 'The Journal of the Anthropological Institute of Great Britain and Ireland,' 1901, "Man," p. 49.

[2] Of the type published as "H. 34" in 'Nagada and Ballas.'

[3] W. M. Flinders Petrie and J. E. Quibell, 'Nagada and Ballas,' 1896.

length, with head-rest, the bodies were all contracted and accompanied with jars of ashes.

In 1896 Professor Petrie's view was that the "new race" was a foreign one which entered Egypt probably after the Sixth Dynasty, which terminated about 3322 B.C., and before the rise of the Eleventh Dynasty which ruled the Thebaid in the Egyptian manner from about 3006 B.C. The dominion of the invaders probably covered three centuries—3300 and 3000 B.C. Their relations were probably purely hostile, and they probably expelled the Egyptian population from this part and occupied the Thebaid alone.

Not long afterwards Professor Petrie saw reason to believe that the "new race" was pre-dynastic.

This discovery arose from the exploration of the cemeteries of Abadiyeh and Hu.[1] In 'Diospolis Parva' he writes: "In 1897–8 the final proof that the 'new race' remains were pre-dynastic was reached at Dendereh, where I worked through a cemetery ranging from the sixth to the eleventh dynasty, and so finally ejected the 'new race' remains from the only dynastic period they could have occupied, thus by exclusion proving their prehistoric age." Though "pre-historic," the race was not barbarous. Throughout the whole of the pre-historic age stone vases are abundant. As to its length, 2000 years would be more likely than 1000.

Professor Petrie's conclusion is that Egypt was occupied by palæolithic hunters until the beginning of the Nile deposit, about 7000 B.C. Then came in a Libyan race, already pastoral and probably agricultural, making pottery and knowing the use of copper. These people in a century or two developed a profusion of fine hand-made (*i.e.* not turned on the wheel) pottery. Later on in the prehistoric age the pottery grew rough, coarse, and degraded in form. So far Professor Petrie.

The view of the Libyan origin of the ancient Egyptians appears to have been put forward as long ago as 1861 by Pruner Bey,[2] and has been variously received.

Amongst British writers MacIver and Wilkin have tested the hypothesis by comparing the skull and head measurements of modern Kabyle (*i.e.* Berber) individuals with the skulls of the

[1] 'Diospolis Parva,' 1901.

[2] Capart, 'Man,' 1901, p. 84.

prehistoric Egyptians. As a result these authors[1] state that such measurements do not afford the smallest support to the theory of a Libyan element in the early population of Egypt, that the cephalic index absolutely forbids any identification of the prehistoric Egyptians with the Berbers.

This subject has again been adverted to by Arthur Thomson and D. Randall MacIver in their recently published work on 'The Ancient Races of the Thebaid,' 1905.

These authors observe that the evidence shows clearly that the population of Upper Egypt was not composed of a single race-stock, but even in the earliest days was made up of diverse elements. "This disposes of the long-continued dispute as to the 'Caucasian' or the 'African' origin of 'the Egyptian race.'

"The facial skeleton shows two distinct groups, one negroid and the other non-negroid. As regards the negroid element the immediate proximity of Nubia to the geographical area under consideration naturally suggests an influence from that quarter. With the non-negroid stock the problem is more difficult. It might have been affiliated to the Berber-Libyan, to some other Mediterranean, or to a Semitic stock. The question is one on which no definite pronouncement can yet be made. The conclusions arrived at are destructive of the Libyo-Egyptian theory in the form put forward by the authors of 'Nagada and Ballas.' The foundation of the theory was the idea that the archaic population differed from that of later times. We have found that, on the contrary, the component factors were the same from first to last, and the negroid, which is certainly a non-Libyan element, is represented in its strongest form in the earliest periods. During the pre-dynastic periods the negroids were the social equals of the others."

After this brief historical introduction let me describe the calculus itself. About half of the white phosphatic crust enveloping it was broken off by the workman's pick, and its extreme friability subsequently led to extensive fracture in the process of transit, the harder "body" being as a result completely isolated. In the comparatively intact condition when first seen by the donor, the concretion was ovoidal in form and quite smooth on the surface. As far as can be told by the

[1] 'Libyan Notes,' 1901.

readjustment of the fragments, the calculus had an extreme diameter of 6·5 cm. Its chief bulk consists of a white friable phosphatic crust averaging about 1·3 cm. in thickness.

The crust is distinctly laminated, and moreover presents in places, where the fractured surface is uninjured, a distinct vertical or radial crystalline striation. The body of the calculus is of flattened oval form, with a granulated exterior, wanting,

FIG. 48.

Showing a large fragment of the phosphatic crust, partly surrounding the flattened oval body of the calculus. The surface of the "body" is irregularly granulated; its fracture is sharp and both radially and concentrically striated. At the higher end a portion of the nucleus is exposed by the loss of the surrounding part of the body. The specimen is in the Museum of the Royal College of Surgeons. (Photograph of natural size.)

EXPLICATIO FIGURÆ.

Calculus in sepulchro prehistorico Egyptio repertus. Ex substantiâ constat fulvâ et confertâ cujus superficies fracta strias et radiales et concentricas ostendit. Calculus tegmine crasso calcii phosphatis et ammonii magnesiique phosphatis circumdatur. (Magnitudinis naturalis.)

however, the regular tuberculation characterising the mulberry variety of an oxalate concretion. Its fracture exhibits both

a fine radial and a coarser concentric striation, and is of a pale fawn colour.

Where portions of the body have been detached the smooth surface of a nucleus is exposed. This nucleus was afterwards isolated in the process of sawing the calculus. Its divided surface has the same colour as the body, but in construction it wants the compactness and regularity of the latter; and, except at the periphery, it is honeycombed with spaces, the walls of which present a finely granular character. That these defects are not due to accidental losses, but represent irregularities obtaining during the actual process of growth, is obvious from

FIG. 49

The most central, separable portion, or nucleus of the calculus, in section, showing in places a honeycombed or open texture such as is not uncommon in calculi of uric acid. (Photograph, very slightly enlarged.)

EXPLICATIO FIGURÆ.

Calculi præcedentis nuclei sectio; locis in diversis conspicuntur lacunæ ut in calculis quibusdam ex acido urico constantibus.

the fact that the laminæ constituting the most peripheral part of the nucleus are correspondingly distorted or sinuous.

Mr. H. R. Le Sueur was good enough to make a qualitative analysis, with the following result:

Crust.—Moisture (loss at 100° C.), 1·97 per cent.; organic matter (loss on ignition), 32·70 per cent. It readily fused in the flame of the blow-pipe. Bases: Calcium, magnesium, ammonium. Acids: Phosphoric, a trace of carbonic, and a certain amount of uric.

Body.—Bases: Ammonia, sodium, and a trace of calcium. Acids: Uric. On ignition, only a very small amount of ash was left, which consisted for the most part of sodium carbonate. In the nucleus the murexide test showed the presence of uric acid.

Microscopic examination.—Of the body I was able to prepare a microscopic grinding, though only with considerable difficulty, owing to its friability.

The preparation was made by rubbing a fragment, without the use of water, upon a hone, cementing the ground surface to a slide with Canada balsam, and then rubbing from the opposite aspect until the grinding was sufficiently thin to allow the light to pass through: the preparation was completed by means of xylol balsam and cover-glass in the usual manner. The section was made in the radial direction—*i. e.* in a plane at right angles to the outer surface of the fragment selected. The study of such a section reveals a somewhat coarse crystalline construction, of columns which lie in close apposition without intervening material and have a strictly radial disposition. In colour the section is of a straw yellow. The crystalline columns are crossed in the circumferential direction, but without their individual continuity being destroyed, by a series of narrow, somewhat opaque, curvilinear or slightly undulatory lines. These lines are continuous through the different series of laterally opposed crystalline columns, and vary in the degree of their closeness. Under a high power the lines in question are resolvable into fine granules; it also then appears that the intervening transparent areas of the columns hold a certain number of similar granules; they pervade, in short, the whole thickness of the section. By direct light the opaque lines have a reddish-brown colour, and they may be regarded as granular urate involved and included in the crystalline formation of uric acid.

When the action of caustic potash solution is studied beneath the microscope upon crushings of the body, the sharply-edged crystalline fragments are seen to clear up and eventually become quite transparent from the solution of the uric acid, whilst at the same time there is disclosed a homogeneous, transparent yellowish or reddish-brown matrix retaining the original form of the individual fragment; in some such fragments the coarse crystalline columns are still discernible in the deuricised matrix.

In all its microscopical characters, therefore, the body of the calculus, though of such antiquity, behaves in the usual way, the animal matrix, such as is normally present in a uric acid calculus, having suffered no destruction.

Similar crushings of the nucleus show coarsely columnar crystalline fragments like those of the body, and, in addition, compact groups of pale yellow crystals, clearly aggregations of uric acid like those which may be encountered in microscopic sections of uric acid calculi.

The absence of oxalate both chemically and in the microscopic section is of some interest. For in regard to the microscopic evidence I may observe in passing that the presence of calcium oxalate in sections of urinary calculi is recognisable with the greatest ease by reason of its characteristic crystalline structure and transparency.[1]

In regard to the geographical distribution of calculi of the uric and oxalic series, Hirsch [2] observes that one kind predominates at some places and the other elsewhere, these differences being explained chiefly, if not exclusively, by differences in the dietetic factors upon which the production of the "calculous diethesis" depends. We have to think, he says, of a direct production of oxalates in consequence of the habitual use of food or drink producing oxalic acid. In England statistics show calculi of uric acid or urates to constitute 72 per cent. of the whole. In Egypt they at present form only 50 per cent. (Pruner). And it is noteworthy that in India, where the diet of the natives is almost exclusively vegetable, 70 per cent. of the calculi examined were oxalate (Vandyke Carter).

The relation of oxalate calculus to the ingestion of vegetable food appears also, I may observe, in the occasional formation of intestinal calculi of calcium oxalate in herbivora. There are some excellent examples of such in the Museum of the Royal College of Surgeons, the largest of them no less than five inches in diameter.

Such calculi, which were first recognised by Taylor and described in the College catalogue of calculi (1842), in all respects

[1] W. M. Ord and S. G. Shattock: "The Microscopic Structure of Urinary Calculi of Oxalate of Lime' (with micro-photographs) 'Path. Soc. Trans., vol. xlvi, p. 91.

[2] 'Geographical and Historical Pathology.'

resemble the smooth-surfaced urinary forms occurring in man, except that they all present a spherical or oval nucleus of closely matted vegetable fibre. Some are of almost pure oxalate of lime, others admixed with calcium carbonate.

With the progress of vegetarianism the formation of intestinal calculi of calcium oxalate in the human subject is, as I have elsewhere observed ('Path. Soc. Trans.,' vol. xlvii, 1896, p. 102), a phenomenon to be anticipated and looked for. As an approach in this direction, I may mention, in passing, that the presence of this substance has been recently shown by Mr. L. S. Dudgeon in a calculus removed by Mr. Makins from the vermiform appendix. This calculus, which is somewhat oval, 1·2 cm. in chief diameter, and irregularly tuberculated at either pole, contains calcium and magnesium combined as carbonate, phosphate, or oxalate; the wall of the appendix was much thickened and indurated from chronic inflammation; the patient was a policeman, and a hearty eater of meat and vegetables.

It is generally held by physiologists that the chief part, though not the whole, of the oxalate present in the urine is derived from that ingested in vegetable food-stuffs.

During the later dynasties the staple food of the ancient Egyptians was vegetable, viz. wheat, barley, peas, lentils, many fruits, with dates and small plants.[1]

That the prehistoric Egyptians, however, were not such strict consumers of vegetable foods is clear from the discovery in the prehistoric graves of such objects as hunting-lances of flint. And to these evidences may be added the discovery made by MacIver at El Amrah, of the clay models of kine in three of the prehistoric graves explored ('Man,' 1901, p. 50); and for a more detailed account see 'El Amrah and Abydos, 1899–1901,' D. Randall MacIver, M.A., and A. C. Mace, with a chapter by F. Griffith, M.A., F.S.A. (special extra publication of the Egyptian Exploration Fund, 1902).

The absence of calcium oxalate in the calculus under consideration, therefore, offers no difficulty.

The great frequency of calculus in Egypt in modern times is notorious. Mr. F. R. S. Milton, speaking from his experience as

[1] See a note, furnished by Mr. F. C. I. Spurrell, accompanying a paper by Mr. F. S. Eve, 'Path. Soc. Trans.,' vol. xli, p. 242, on specimens of osteoplastic periostitis, etc., from Egyptian mummies.

surgeon to the Kasr-el-Ainy Hospital, Cairo, states that the cases admitted reach a yearly average of about 150.[1]

That this is not merely a frequency of quite recent times appears from the work of Professor Alpinus ('De Medicina Egyptorum, 1719),[2] who notices the same fact, particularly in regard to Lower Egypt. Of writers intermediate between Alpinus and Milton a number might be cited to the same effect.

The commonness of calculus is connected by many recent writers with the Bilharziosis at present so widely spread at the coast and by the banks of the Nile within the Delta. Milton (*loc. cit.*) remarks that in practically all the cases of calculus ova are either present in the urine, or there is a history of Bilharzial disease within the time necessary for the formation of the calculus.

The parasite occurs but rarely in the female sex; and as regards age, the symptoms almost invariably show themselves before puberty.

In both these last respects the calculus from the prehistoric grave at El Amrah bears out the possibility of having been associated with Bilharzial disease, seeing that the skeleton, in the pelvis of which it lay, was that of a boy, aged about 16 years. Notwithstanding these possibilities, however, a very protracted examination of the specimen has quite failed to demonstrate the presence of Bilharzia ova.

And having regard to the indestructibility of chitin by natural means, and its insolubility in caustic alkalies, I feel satisfied that the examination of the uric acid nucleus, made both with and without the use of caustic potash, would have revealed the capsules of the ova had they been there. The indestructibility of the capsules in hydrochloric acid allowed, moreover, of a complete examination of microscopic crushings of the phosphatic crust, but this was attended with an equally negative result.

Yet so great a need for caution in the interpretation of certain appearances did the examination disclose, that I venture to state in conclusion how the search for the ova was carried out; and without checks made from preparations of the ova themselves error might certainly have arisen. The check preparations consisted of sections of the vesical wall with imbedded ova, and

[1] "Lectures on Bilharzia" ('Journal of Tropical Medicine,' 1902, p. 200).

[2] Cited by Hirsch, 'Geographical and Historical Pathology.'

scrapings from the divided surface of a Bilharzial lesion, the ova so obtained being treated both with caustic potash and hydrochloric acid. The slides, cleaned in spirit and wiped dry, were washed over the surface to be used, with water filtered directly from a cone of paper held in forceps, without the use of a funnel. The material from the nucleus was obtained by boring with the point of a knife, previously heated over the flame and plunged into alcohol, the spots selected being the lacunæ present in the nucleus, and its actual centre: the *débris* was received as it fell, directly on to the wetted slide. With a glass rod, over which water had been first allowed to filter, the *débris* was finely crushed by rolling the rod backwards and forwards on the slide; portions of the turbid fluid resulting were transferred to a series of other slides and the several preparations completed with cover-glasses.

The examinations were first made of the slides as so prepared; a drop of caustic potash was afterwards allowed to fall from a cone of filter-paper on to the slide at the edge of the cover-glass. In the case of the phosphatic crust pure hydrochloric acid was added with a clean glass rod. The preparations were studied as the reagents mentioned dissolved either the uric acid or the calcium phosphate. Amongst the objects to be excluded in such preparations, from fragments of Bilharzial capsules are: scales of glass detached from the rod in rolling the fragments of the calculus (distinguishable by their rigidity when the preparation is tapped or pressed with the needle); epithelial cells, distinguishable by their relatively small size when compared with the Bilharzial ovum; transparent flakes of the matrix of the calculus, or spheroidal portions of the transparent matrix of fragments, which appear after the removal of the uric acid with caustic potash.

Never have I seen a body which in size and physical appearance corresponded with the capsule of the ovum, and never have I seen any indication on any ambiguous fragment, of the Bilharzial spine, so characteristic (in the Egyptian parasite at least[1])

[1] Dr. John Catto has described and figured a new form of Bilharzia, or Schistosoma hæmatobium (*Schistosoma Cattoi*), of which the ova are quite destitute of spine. In this particular case the lesions were limited to the alimentary system. The parasite was discovered in a Chinaman who died of cholera in a passenger ship from China, the patient having, presumably, never been away from China before. ('British Medical Journal,' January 7th, 1905; and in this volume of the 'Pathological Society's Transactions.')

that the diagnosis could have been made with certainty on its presence and must be excluded on its absence.

Examination of a second ancient Egyptian Calculus.

Since concluding the foregoing observations upon a predynastic vesical calculus, I have been enabled through the kindness of Professor Elliot Smith to examine a second calculus of somewhat later date.

This calculus was found, together with three others, by Pro-

FIG. 50.

A tuberculated renal calculus (one of four) from a tomb of II. Dynasty. The dark areas shown in the photograph are due to yellow staining (natural size). In its centre was an extensive cavity full of mould conidia, but containing no Bilharzia ova. Chemically the calculus was found to consist of carbonate and phosphate of lime with a certain amount of calcium oxalate.

EXPLICATIO FIGURÆ.

Calculus tuberculatus ex calcii carbonate, calcii phosphate, et calcii oxalate constans qui in sepulchro Ægyptio dynastico (II) repertus est. Intus adest loculus, fungi conidiis plenus. Nulla adsunt ova Bilharziæ hæmatobii. (Magnitudinis naturalis.)

fessor Elliot Smith in a grave of the II Dynastic period excavated at Naga-ed-dêr (near Girga, Upper Egypt) by Dr. George A. Reisner on behalf of the Egyptological expedition of the University of California, subsidised by Mrs. Phœbe Hearst.

As they were found lying alongside the first lumbar vertebra, it may be assumed that they are renal.

Though coming from a second Dynasty tomb, their age is computed to be only about six hundred years later than that of the prehistoric calculus first described. The particular calculus sent to me is 1·6 cm. in extreme diameter and has the mamillated or tuberculated exterior suggestive of the mulberry variety of calcium oxalate. The general surface is white and chalky in consistence. Here and there a deep yellowish-brown area occurs, but the coloration is due merely to staining, as the most superficial scraping at once brings into view the white powdery substance of the general surface.

Upon cutting away from one of the flatter sides I unexpectedly opened a central cavity, which, on being probed with a needle, proved to be quite extensive, the calculus itself being hardly more than a fragile shell. The broken surface is concentrically laminated in a somewhat coarse and irregular manner and of a dull white colour.

Mr. H. R. Le Sueur, on analysis of material comprising the entire thickness of the calculus, found calcium, combined with carbonic, phosphoric, and oxalic acids. The material, on being dissolved in dilute hydric chloride, effervesced in a marked degree; an undissolved organic residue was filtered off; this contained no uric acid. The clear filtrate, on being made alkaline with ammonia, yielded a voluminous precipitate, most of which dissolved on the addition of acetic acid, proving it to be phosphate. A small residue, however, of finely crystalline material remained this represented the calcium oxalate of the calculus.

The crystals I found to consist, not of octahedra, but the less common form of square prisms with pyramidal ends, or elongated tablets with parallel sides and obtusely pointed extremities.

Such forms are figured from calculi of oxalate of lime by Dr. Vandyke Carter ('Microscopic Structure of Urinary Calculi,' 1873, Pl. III) and by Dr. Ord ('The Influence of Colloids upon Crystalline Form,' 1879). The latter author had only twice seen flattened tablets of calcium oxalate in the urine, which in each case was albuminous, but he was able artificially to produce such in gelatin (Plate V, fig. 6). Excellent figures of this variety of crystal are given in the more recent 'Atlas' of Rieder and Delépine (Pl. I, figs. 4 and 6).

The cavity was loosely filled with a soft, dry, chocolate-coloured material, which was detached by needling, and removed by

inverting the calculus. Microscopical examination was made in the manner already detailed. The calculus itself evolved carbonic acid in large amounts on the addition of hydrochloric acid. No Bilharzia ova were present. As the soft material from the central cavity was the most promising, I made a large number of examinations of this in search for ova. The substance was readily disintegrated by rolling it in distilled water on a slide by means of a glass rod. Every preparation displayed great numbers of mould conidia but no Bilharzia ova. So well preserved were many of the conidia that I carried out the following test to see if perchance any were still living.

March 23rd, 1905.—I inverted the calculus over a sterilised watch-glass, and scratched the interior of the central cavity with a sterilised needle. A Petri dish, into which a specially thick layer of agar had been poured and allowed to set some hours previously, was then inoculated with the platinum loop, the loop, after sterilisation, being first wetted with the water condensed on the lower side of the cover, and then dipped into the fine brown powdery material in the watch-glass. With a red "china pencil" a series of spots had been marked on the under surface of the lower glass of the Petri dish, and over them the agar surface was inoculated from a succession of loops. In order to prevent drying of the medium the dish was placed in a Pakes's crate, and the crate itself was lowered into one of the amber-yellow jars with ground top and cover devised by myself not only for this purpose, but also to obviate any deleterious action of sunlight if the incubator were not used; at the bottom of the jar a circle of filter-paper wetted with sublimate solution had been first laid. The apparatus was kept in the incubator at a temperature varying between 25° C. and 30° C. No growth of any kind took place from the inoculated spots and none elsewhere, although precisely similar needlings of the interior of the calculus had yielded microscopically an abundance of conidia. The capsule remained absolutely sterile. The last observation was made July 24th, 1905, when the agar was quite moist, and the surface and substance of the medium quite sterile, the inoculated material being still evident upon it: a microscopic examination of the latter at this date revealed large numbers of conidia.

April 4th, 1905.

28. *Suppurative periostitis following typhoid fever.*

By W. H. Battle and L. S. Dudgeon.

There are now many instances of the occurrence of bone lesions after typhoid fever in the discharge from which the *Bacillus typhosus* has been demonstrated. There are some unusual features in the following case which make it of exceptional interest. Most of those recorded have been affections of the tibiæ or ribs, and the area of bone involved has not been so extensive as here. It is unusual, also, to have an inflammation. It is noteworthy that, although the periosteum was completely separated from the bone for some distance up the shaft and in the whole circumference, the recovery of the limb without necrosis of bone has apparently been assured.

The patient was admitted into the Leopold ward of St. Thomas's Hospital on October 28th, 1904, and was discharged on December 21st, 1904. The following history of the case is taken from the notes by Mr. Finch: The patient was in George ward, under the care of Dr. Hector W. G. Mackenzie, from July 7th to September 10th, 1902, suffering from typhoid fever. The illness had commenced on June 30th, with headache, vomiting, and pain in the back and abdomen. On July 11th, symptoms of perforation developed at 1.30 p.m. Abdominal section was performed at 7.15 p.m., and a perforation of the ileum was sutured by Mr. Battle. The patient was re-admitted, on September 18th, for pain in the right femur and knee, which was treated with iodide of potassium and local applications, and he was able to leave the hospital in about three weeks. Since that time he had been in good health, but was re-admitted some months later for pain in the abdomen which followed a slip whilst carrying a sack of coals. The present illness began four weeks before admission, with pain in the lower half of the right femur. The pain was of a gnawing character, sometimes shooting down the leg; it was worse at night, and kept the patient awake.

On admission, the lower third of the right femur was uniformly

enlarged, and was extremely tender on pressure. The skin in front of the thigh in this situation was red from the application of mustard poultices before he came to the hospital. His temperature was 102·2° F. There was no evidence of syphilis; the glands in both groins were easily felt, and there were a few scars on the legs, which were not characteristic of any special lesion. Skiagrams showed thickening of the lower half of the femur. On November 3rd, the pain was stated to be somewhat better than on admission; the patient perspired freely at night, whilst the temperature varied from 100° to 101° in the day. Iodide of potassium in increasing doses was given without any benefit. The severe pain continued and the temperature remained elevated, not below 99° in the morning or above 101° in the evening. No apparent change had taken place in the condition of the bone, which continued to be extremely tender and uniformly enlarged. On the 16th, an incision was made on the outer side of the thigh above the knee. Thickened periosteum was incised, and thick yellow pus immediately sprang into the wound. The periosteum was separated from the shaft all round, and the exposed bone was found to be roughened. The operation wound was drained, and the pain was quickly relieved by the incision. When the patient left the hospital the wound was soundly healed, and he has now resumed his work.

Bacteriological report.—A culture-tube of broth was inoculated with the pus from the periosteal abscess, and incubated at 37° C. for twenty-four hours. Marked turbidity and a slight flocculent deposit in the culture-tube were observed at the end of the first twenty hours. Film preparations were made from the culture and were stained by Gram's method. Short thin bacilli, which were Gram negative, were seen in the films. The original culture was now plated on the surface of jelly by the stroke method. Large numbers of pale bluish-white colonies with an irregular margin, and gradually sloping from the centre towards the periphery, were seen on the surface of this medium at the end of twenty-four hours at 22° C. These colonies were found to be similar in most respects at the end of forty-eight hours. We consider this to be a fact of very great importance, as although the surface colonies of certain strains of the colon bacillus are very similar to the colonies of the *Bacillus typhosus*, yet the surface colonies at the end of forty-eight hours are quite different,

owing to the much more rapid growth of the colon bacillus. The surface colonies of the colon bacillus at the end of forty-eight hours are much denser and darker than the typhoid colonies, the irregular margin is much more opaque, and the colonies, instead of gradually sloping from the centre towards the periphery, as in the case of the Bacillus typhosus, terminate abruptly, and thus give quite a different appearance to that which is seen at the end of twenty-four hours. Numerous colonies from the surface of three gelatin plates were emulsified in 0·85 per cent. solution of normal saline, and the emulsions were then tested with positive typhoid serum. The bacilli from each colony were found to be actively motile, while on the addition of typhoid serum, using a dilution of 1 in 50, complete loss of motility and complete "tight" agglutination were obtained in the case of every colony which was examined. The agglutination of the bacilli and the complete loss of motility took place immediately. We consider this means of examining colonies of suspected typhoid bacilli to be of the utmost value, as we have never seen agglutination of the *Bacillus coli*, with positive typhoid serum such as occurs in the case of the *Bacillus typhosus*, or even with dilutions of 1 in 10, although we have examined some hundreds of strains of the colon bacillus, chiefly obtained from the peritoneal cavity. It must be remembered that by this means valuable information can be obtained at the end of twenty-four hours regarding the nature of a suspected bacillus. Three of the surface colonies from the jelly plates were subcultured into broth, and afterwards large numbers of tubes of various media were inoculated from these broth tubes.

The following are the cultural characteristics of this bacillus:

Agar.—Pale streak, with a slightly irregular margin and moist surface. The streak became more opaque and the growth more extensive as time advanced.

Glycerine agar.—Very similar to the growth on agar.

Glucose agar shake.—There was no gas production at the end of one month's growth at 37° C.

Gelatin slant.—Slight pale bluish white streak with a feathery edge was seen at the end of twenty-four hours' growth.

Neutral red jelly.—Appearances of growth similar to those seen on jelly. No alteration of colour and no liquefaction of the medium had appeared at the end of one month.

Glucose jelly shake.—No gas formation had occurred at the end of one month's incubation.

Litmus mannite jelly shake, litmus cane sugar jelly shake, litmus maltose jelly shake, and litmus lactose jelly shake at 22° C. —The colour of the litmus was unaltered, and there was no gas production.

Litmus milk.—This medium was acidified at the end of three days' growth at 37° C., but the milk was not even thickened at the end of one month.

Milk.—Unchanged.

Potato.—Very slight moist pale growth formed on the surface of potato in forty-eight hours, but it never increased.

Peptone water.—No indol production at the end of fourteen days.

Neutral red broth.—A good growth was seen in this medium, but there was no alteration of colour at the end of one month.

Glucose broth (*anaerobically*).—Good growth without any production of gas.

McConkey's medium. — Sodium-taurocholate-litmus-glucose broth culture-tubes were inoculated with the bacillus in question and then incubated anaerobically at 42° C. The medium was acidified in forty-eight hours, but there was no evidence of any gas formation.

Agglutination tests.—*With positive typhoid serum:* Dilutions 1 in 20 and 1 in 50: complete loss of motility and complete "tight" agglutination occurred immediately with each dilution. Dilution 1 in 100: similar result at the end of thirty minutes. *With patient's serum:* Dilution 1 in 20: diffuse loose clumping and slight loss of motility in thirty minutes. Dilution 1 in 50: very slight loose clumping and very slight loss of motility at the end of thirty minutes.

Professor W. Osler[1] mentions that six cases of "bone lesions" came under his notice among the sequelæ of typhoid fever in the course of one year. In this country, however, bone lesions directly due to the typhoid bacilus appear to be rare. In Keen's monograph on the surgical complications and sequelæ of typhoid fever he gives the bacteriological report of 51 cases of the bone lesions of typhoid fever. In 38 instances the *Bacillus typhosus* was recovered, while in 13 examples the more common pyogenic

[1] 'The Principles and Practice of Medicine,' fourth edition, 1901.

organisms were found. The case which we have described is of considerable interest owing to the fact that the bone abscess contained the typhoid bacillus in pure culture more than two years after an acute attack of typhoid fever. There is only one other point to which we wish to draw attention—viz., the agglutinative property of the patient's serum. Mr. H. S. D. Browne and Dr. K. E. Crompton,[1] working in the clinical laboratory of St. Thomas's Hospital, found that out of a total of 68 cases only three gave a positive reaction—*i. e.* complete loss of motility and large tight agglutinations within a period of 30 minutes with dilutions of 1 in 20 and 1 in 50—while of these three cases the patient's serum in one instance was obtained two months after the acute illness had subsided. These authors mention that if they had considered a dilution of 1 in 10 to be a positive reaction then their sum total of positive cases would have amounted to 11, but they very wisely refrain from including such low dilutions amongst their positive results. Fison[2] has stated that he has obtained a positive reaction with dilutions of 1 in 2 and 1 in 9 in 18 out of a total of 21 cases examined three months to eight years after the primary illness. Rénard[3] examined 104 cases, 35 of which gave positive reactions, in five instances 20 years after the attack. This observer, however, was content with a dilution of 1 in 10, except in one of his cases in which a dilution of 1 in 40 was employed. Dr. C. G. Seligmann[4] failed to obtain a positive reaction, even with a low dilution of 1 in 20, in Dr. H. C. Jonas's case of multiple typhoid abscesses two years after the original attack. It must be quite obvious, however, that although positive reactions with such low dilutions may be of some interest they cannot be of the slightest practical value. Mr. Browne and Dr. Crompton have definitely shown that it is quite the exception for the true positive typhoid agglutinative reaction to last for more than a short period after the acute illness has subsided, and that it does not remain for months or even years afterwards, as is so often incorrectly taught. Our own experience is in accordance with the views of these observers.

[1] "Note on the Persistence of the Gruber-Widal Reaction in Convalescence from Typhoid Fever," 'The Lancet,' June 27th, 1903, p. 1798.

[2] 'Brit. Med. Journ.,' July 31st, 1897.

[3] 'Thèse de Paris,' 1902.

[4] 'The Lancet,' October 4th, 1902, p. 931.

29. *A phosphatic vesical calculus formed on an ear of wheat-straw in a male.*

By WILLIAM H. BATTLE.

THE patient, a Berkshire shepherd, aged 65 years, was sent to me by Mr. W. Raalfe-Cox and admitted to St. Thomas's Hospital on October 20th, 1904.

He had complained of irritability of the bladder for a year, with pain and hæmaturia. There had also been an occasional stoppage of the stream during micturition, and six months ago he passed a small stone. For six months the urine has been dark-coloured, with the presence of blood.

There was more blood at the end of micturition than at the starting of the act. The pain was of a burning, pricking nature and was continuous, though worse on micturition; it did not radiate, but remained localised in the perineum and penis. Micturition was very frequent both day and night. He had been in a hospital but was dismissed as incurable. He was told that he had cancer of the bladder.

Examination showed the presence of a stone, which was fixed in the neck of the bladder so that only a small sound could be passed beyond it—not a large one. This stone was easily felt in the position of the prostate on rectal examination. The urine, passed in scanty amounts, was alkaline and contained much pus, blood, and mucus. No fragments of new growth were found on microscopical examination.

The stone was removed by supra-pubic operation on October 26th. It was wedged in the neck of the bladder, and lifted from its position with some difficulty. The mucous membrane on the floor of the bladder was ulcerated and bled freely as the stone was extracted.

The patient made a good recovery, left the hospital December 1st, 1904, and has remained well since.

The calculus, which measures an inch and three quarters in its longer diameter, weighed 32·75 grms., is ovoid in shape, of fairly smooth surface, and whitish appearance. On section, it presents two parts—a nucleus and envelope, as shown in the figure.

The envelope consists of white, chalky-looking layers of some-

what soft consistence. This on chemical examination was found to be calcium carbonate and ammonio-magnesium phosphate.

The nucleus is seen to be formed by an ear of wheat-straw.

The explanation of the presence of this piece of straw in the bladder, given by the patient, is that a year ago, before there was anything wrong with him, some farm hands put a piece of

FIG. 52.

Phosphatic calculus formed on an ear of wheat-straw. (Natural size.)

straw in his pipe when he was drunk—"for a lark like"—and that the straw had not come back.

It is probable that the straw was pushed into the urethra with the glumes lying against the stem, the attached ends being towards the bladder, that they opened up when in the urethra, and that the blade of straw ascended to the bladder as an ear of barley will reach the shoulder when placed in the sleeve.

April 4th, 1905.

30. *A case of subacute atrophy of the liver.*

By S. G. Scott.

De atrophiâ hepatis subacutâ.

Summarium.

Femina anno ætatis 23, octo menses ictero ægrotaverat.

Diagnosis obscura.

Sectione abdominis explorativâ factâ insigne nil inventum est. Mox autem hæmorrhagia continua subsecuta est propter quod ægra mortua est.

Post mortem repertum est hepar parvum (pondere 625 grammes), molle, et rugosum.

Sectio rubra erat cum maculis flavis variata.

Conspectu microscopico partes flavæ cellulis hepaticis morientibus mortuisque constare inventæ sunt.

Fibrosis nulla adfuit.

Partes rubræ ex telâ connexivâ constant in quâ multæ sparguntur cellulæ "plasma" et "mast" ut dicuntur.

In hac telâ multi jacent tubuli in annulis ordinati.

Hi tubuli, contorti et ramosi, originem de minimis ductubus felleis capiunt; fel continent, sed cæce terminantur; fines tubulorum cæcæ ad annulos medios vertuntur. In tubulorum annulo medio vena sæpe discernitur. In parte tubulorum externâ cellulæ illis ductuum felleorum similes sunt; in parte autem internâ prope finem cæcam, cylindricæ sunt cellulæ, atque fel et pingue continent.

Hæ cellulæ illis hepatis dissimiles esse videntur, tamen sicut cellulæ hepaticæ vere se gerunt.

Putat igitur auctor hos tubulos hepatis telam regenerare.

Si ex operatione femina non mortua esset, forsitan se recuperasset, at cum telæ hepaticæ regeneratione cirrhosis probabiliter conjuncta esset.

The patient was a young unmarried woman, aged 23 years, who was admitted to the General Infirmary at Leeds under Mr. Mayo Robson, on March 14th, 1903, complaining of jaundice. The history was as follows:

She had always been strong and healthy until a year or two before her death. For five years before August, 1902, she had been in domestic service, and during the last year or so of that time had been liable to occasional attacks of vomiting, with severe pain, attributed by her then medical man (now dead) to indigestion.

Early in August, 1902, having left her situation, *not* on account of ill health, she consulted Dr. Crerar, of Maryport, on account of urticaria of the legs. At that time there was slight jaundice whose onset had probably been gradual. By August 18th there was well-marked jaundice. On September 16th there was a note to the effect that liver dulness did not extend to the costal margin. She then went to the Carlisle Infirmary, where she stayed four weeks, and was treated for catarrhal jaundice. Dr. Crerar did not see her again until January, 1903, when she was still jaundiced, the jaundice having continued to a greater or less degree ever since August.

Dr. Crerar was kind enough to make special inquiries for me as to the possible syphilitic infection or pregnancy, but found no evidence of anything of the sort.

The notes taken at the Leeds Infirmary record that there had been no attacks of pain since the beginning of the jaundice. She had vomited occasionally during her illness, but for the last fortnight before admission almost every day. The fæces had been clay-coloured throughout.

On admission nothing could be made out on abdominal examination and no abnormality could be detected apart from the jaundice. The urine was free from albumen and sugar, and contained bile-pigment; there is no mention of leucin or tyrosin.

The diagnosis was obscure, and Mr. Robson tells me that he did not feel inclined to operate, but, on account of the earnest desire of the patient's relations that he should do something if possible, he made an exploratory laparotomy on March 17th.

The gall-bladder was found distended with bile, and was aspirated. No stones were found within it. A drainage-tube was then stitched in. There were no stones in the ducts. On palpation of the pancreas it felt as if there were a miniliform thickening along the duct. The ampulla of Vater was explored through an incision in the duodenum, but nothing abnormal was found except an apparent thickening and hardness of the head of the pancreas. After sewing up the duodenum the abdomen was closed round the drainage-tube. A bacteriological report states that the bile was sterile.

After the operation Mr. Robson was inclined to think that the case was one of chronic pancreatitis. During the night the patient became collapsed and blanched. The fluid from the tube was deeply blood-stained, and there was hæmorrhage into the dressings round the tube. Sixty grains of calcium chloride were given in an enema. Next day she was very weak, but improved somewhat after infusion with three pints of saline. She was infused again at 5 p.m., with little benefit. Calcium chloride was being given four-hourly in large doses. Death occurred at 11.30 p.m., March 18th, as a result of the continuous bleeding.

Autopsy, 13½ hours p.m. (Dr. E. F. Trevelyan).—The body was jaundiced throughout. There were subserous hæmorrhages scattered over the thoracic and abdominal viscera, and a little blood in the peritoneum. The pancreas was normal to the naked eye and microscopically.

The liver was soft and small, its capsule was somewhat wrinkled, and it weighed 625 grm. (22 oz.). On section the cut surface was homogeneous in texture and salmon-red in colour, with numerous round gamboge spots scattered over it, varying in size from a pin-head to a centimetre.

Pieces were fixed in 10 per cent. formalin, and cut in paraffin. Other pieces were transferred from formalin to Müller's fluid, and after treatment by Marchi's method were imbedded in paraffin. The principal staining methods employed were: Ehrlich's acid-hæmatoxylin and eosin, Paine's iron-hæmatoxylin,

with or without after-staining in van Gieson's mixture, Unna's polychrome-methylene blue, Pappenheim's pyronin-methyl-green mixture. Marchi sections were stained in safranin.

The gamboge areas consist of islands of liver tissue. The cells in these places are mostly swollen and of granular texture, more homogeneous and less reticular than that of normal liver-cells. They stain more intensely with eosin than do healthy cells, and their nuclei show very little structure. A few of them contain fat. No signs of activity or regeneration are seen in them. The whole appearance is degenerative, and the degeneration is often most marked at the periphery of the patch. The connective tissue in these areas is not increased, and often looks degenerate. In some places there is an appearance at first sight suggestive of fibrosis, but the collagen fibres are too thin for that. A more reasonable explanation is that the liver-cells have disappeared and left the delicate connective-tissue skeleton of the lobule.

The red substance in which these gamboge areas lie has as a basis a very cellular connective tissue rich in plasma-cells and containing a fair amount of mast-cells. Except about the portal tract the connective tissue is nowhere dense. In some places, generally about the portal tract, there are small patches of lymphocytic infiltration. There is no catarrhal inflammation of any bile-duct. In most of the blood-vessels throughout this tissue, in addition to the blood-cells, are many fine granules of dark-brown pigment. This is seen nowhere else.

In a prolonged examination of many sections bacteria were only seen two or three times, two zooglæa masses of cocci plugging capillaries, and a doubtful pair of large diplococci.

Throughout this connective tissue are branching tortuous tubules of epithelial cells, intermediate in size between those of the smaller bile-ducts and liver-cells. These tubes appear to end blindly. Their cells frequently contain fat, and their lumen contains bile.

In the earlier sections examined, where the gamboge areas predominated, the appearances were puzzling, and my idea was that the condition could best be described as an acute cirrhosis, or, histologically, a subacute hepatitis.

When, however, sections from other parts were examined, where there were few or no areas of degenerating liver-cells, it

became evident that the above-mentioned tubes were arranged in rings. These rings I have traced through serial sections for a total thickness of 60 μ. At the centre of them, some little way from the tubules, a small vessel can often be seen.

Closer examination of the tubules then showed that they were in connection with the small bile-ducts outside the rings, and I was soon able to find transitions from these small-celled ducts into the larger-celled tubules. In all these tubules the cytoplasm was reticular throughout. The cells of the smallest perilobular

FIG. 53.

Section showing rings of tubuli around a central vessel, as described in the text.

EXPLICATIO FIGURÆ.

Sectio microscopica tubulos in annulis ordinatos monstrans; in tubulorum annulo medio discernitur vena.

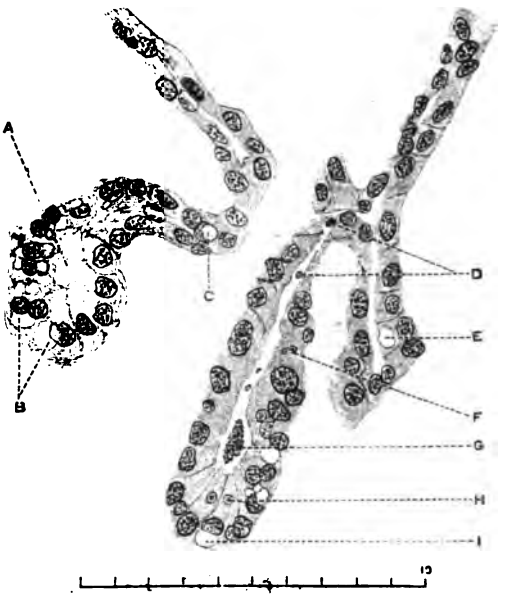
bile-ducts are, as usual, oblong to square on section, being wider from side to side than from base to free surface. Towards the blind end of the tubules the cells get bigger and are more columnar in shape, and it is only in these large cells that the fat is seen. The lumen, too, becomes wider there, and bile is seen to lie in it. Inside the larger cells—that is, cells of the class that contain fat—bile can be seen not infrequently, and some of

the appearances of these cells are suggestive of secretory vacuoles containing bile, and of intra-cellular bile-canaliculi.

The blind end of the tubules is towards the centre of the ring.

I therefore conclude that the rings represent liver lobules and that the central vessel sometimes seen is the intra-lobular vein. These ring systems have no visible connection with the liver

FIG. 54.



Two tubules, showing their origin from small bile-ducts. Towards the blind end the cells are larger and contain fat droplets and bile. A. Expanded lumen at blind end of tubule. B. Fat droplets in cells. C. Lumen of tubule cut across. D. Bile in lumen of tubule. E. Fat droplet in cell. F. Bile in cell. G. Bile in expanded lumen at blind end of tubule. H. Vacuoles holding bile, in two cells. I. Fat droplet. Zeiss apochromatic, 3 mm.; compensating ocular, 6. Drawn with the camera lucida by the author. Each division of the scale represents $\frac{1}{100}$ mm.

EXPLICATIO FIGURÆ.

Sectio microscopica duos tubulos qui ex ductubus felleis parvis oriuntur monstrans. Ad fines cæcas tubulorum cellulæ et fel et pingue continent.

cells of the gamboge areas. There is no evidence of increased formation of new bile-ducts as opposed to the tubules, if the

shrinkage of the liver and absence of liver-cells be borne in mind.

In short, the gamboge patches consist of dead and dying liver imbedded in the red substance, which is full of rings of glandular tubules, arranged around the central vessel. These tubules are continuous with the peri-lobular bile-ducts, contain bile in their lumen, and the larger cells in them contain fat and bile.

Eventually these appearances in the red substance, together with the condition of the yellow part, led me to the conclusion that this was an atypical case of acute atrophy of the liver, one of those cases which do not prove immediately fatal.

My idea of the disease process here is that a poison of unknown nature, but of only moderate severity, attacked the liver. It was of such a nature that it brought about destruction of the liver-cells, but had little or no effect on those of the bile-ducts. The history of previous gastro-intestinal disturbance, and the appearance of fibrosis round the large bile-ducts, seem to indicate that it came by the portal tract.

Anyhow, it cannot have been very virulent, or the patient would not have survived so long as she did, and parts of what I presume to be the original liver—the gamboge patches—would not have survived in a recognisable shape.

Now, since the liver-cells and the bile-duct cells are developmentally the same, both having arisen from the columnar cells of the archenteron, the liver-cells may be regarded as highly specialised bile-duct cells. So when the greater part of the liver had been destroyed the cells of the smallest perilobular bile-ducts began to multiply and rebuild the liver. From the occurrence of bile and fat in many of the largest cells of the tubules, it is, I think, evident that these cells, although they have not the morphological appearances of liver-cells, are yet performing some of their functions.

I regard, therefore, this formation of tubules, and their arrangement in rings, as distinct evidence of regeneration of the liver.

This process of regeneration from the perilobular bile-ducts has been described in a good many of the similar cases recorded.

In a good many of them, however, these outgrowths from the bile-ducts reached up to the inner part of the lobule. Here

they were limited to the outer part. Why they should not have gone further is not clear, bearing in mind the other cases, unless the jaundice from which the patient suffered was a mild catarrhal jaundice, terminating latterly in acute atrophy. Against that view is the fact that she was not too ill to be brought up from Cumberland to Leeds and subjected to an exploratory laparotomy, and, more important, that she showed none of the acute symptoms expected towards the end of such a case. It might be objected to my view as to regeneration that in that case mitosis ought to have been seen in the tubules, but it was not, although the material was fixed comparatively fresh, about fourteen hours after death, and in cool weather. For mitosis is mentioned as being seen in a good many of the recorded cases, particularly that of McPhedran and MacAllum (1) which seems to have resembled this one in its histological features; and it was also seen, but only once, in Meder's (2) first case, although his material was not put into the fixative till forty-eight hours after death.

It may be, however, that, since the patient died from slow bleeding, the cells thus impoverished ceased their multiplication, or that the stimulus to regeneration was but slight, or that the patient had comparatively small regenerative power.

Nevertheless, personally, I do not see how the appearances can be regarded as other than regenerative.

The jaundice I am inclined to attribute partly to the disorganisation of the liver-cells in the gamboge patches and partly to the collapse of the whole organ causing pressure on and kinking of the finer bile-ducts, so damming back the bile formed in the tubules of the regenerating parts.

As to the causation of acute atrophy of the liver, this case gives no further light. All that can be said is that it does not favour Quincke's (8) hypothesis of a flow of pancreatic juice up the bile-ducts, for in that case the bile-duct epithelium should have been destroyed, and there are no microscopical evidences of the fat-necrosis which one might expect if that had taken place.

In its long duration this case exceeds all those that I have had access to, with the exception of those of Stroebe (4), two years; Barbacci (5), one and a half years; Steinhaus (3), nine months. These, however, and two of Marchand's (6) were characterised

by nodular hyperplasia—that is, yellow patches with marked evidence of regeneration, in a darker ground substance, and are thus sharply marked off from all other recorded cases.

The cases which most resemble mine structurally are those of Cullingworth (7), and McPhedran and MacAllum (1). These, however, were of a much shorter duration, about a month; and a duration of three to six weeks appears to be the rule in those cases resembling this one.

Quincke (8) records three cases of recovery from acute atrophy of the liver and quotes Wirsing as having in 1892 collected sixteen recoveries from the older literature. Rolleston (9) quotes Wickham Legge as having, in 1897, collected twenty-eight recoveries.

Recovery, then, is possible, and had the patient survived the operation, then, to my mind, there were three possible alternatives:

Firstly, she might have died later, like an ordinary case of acute atrophy, from progressive destruction of the liver.

Secondly, she might have recovered, owing to there having been sufficient regeneration to give her a comparatively normal liver.

Thirdly, she might have recovered to some extent—and this is the view to which I incline—but *pari passu* with regeneration a cirrhosis would have developed. For, to my mind, the presence of many mast-cells (10), and of plasma-cells indicates a slow inflammatory reaction, going on to fibrosis, and, from the uniform and general distribution of these cells, I think the cirrhosis would have been intra- as well as extra-lobular, possibly a pericellar one.

If I may be allowed to speculate further out of this third alternative, I should like to suggest that some of the unexplained cirrhoses so often met with may be the result of a previous affection of the liver of toxic origin, and, with or without the accompaniment of jaundice, giving rise to some little destruction of liver-cells, and eventuating in fibrosis.

In conclusion, I wish to express my thanks to Mr. Mayo Robson for allowing me to publish the case, to Dr. Crerar, of Maryport, for giving me more details of the previous history than were to be found in the notes, to Professor A. S. F. Grünbaum for obtaining for me some otherwise inaccessible literature,

to Dr. O. Gruner for photomicrograph, and to Dr. W. H. M. Telling for much valuable criticism.

The case is entered as No. 494, in the third edition of 'Diseases of the Gall Bladder and Bile Ducts,' by A. W. Mayo Robson.

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April 4th, 1905.

31. *A case of asymmetrical congenital malformation of the lower extremities.*

By HENRY RUNDLE.

A. H., male, aged 10 years, was admitted into the Royal Portsmouth Hospital in March, 1884, for fistula ani, when photographs were taken, and the following report[1] of an examination of the lower extremities was made:

A well-nourished, healthy-looking boy, in all respects well developed but for the remarkable deformity of lower limbs. The only history obtainable was that he was an illegitimate child, deserted since birth by both parents.

His legs are so short that when he stands erect, with the arms dependent, the tips of his fingers nearly touch the ground. The weight of the body is supported mainly by the right leg, which is the shorter of the two, and there is well-marked talipes equinus of this foot. The left leg is kept in the adducted position, out of

[1] 'Path. Soc. Trans.,' vol. xxxv, p. 317.

the line of the centre of gravity of the body, and the foot of this side is turned outwards, so that when he walks it is on its inner

FIG. 55.

From a photograph of the patient when 10 years of age.

edge, as in talipes valgus. The length of right leg is 9¼ inches, that of left leg 14½ inches. This difference in the length of the limbs is partially compensated by the obliquity of the pelvis,

which is tilted downwards to the right side in a very marked manner, and there is compensatory lateral spinal curvature.

Both limbs can be flexed towards the trunk to an angle of 45°, but not beyond; neither limb can be hyper-extended. The right limb can be abducted very freely, in fact, to a right angle with the trunk, but scarcely any adduction can be performed. The left limb admits but slight abduction, whilst adduction is extremely free.

Measurements.

Right anterior superior iliac spine to tip of right inner malleolus	9¼ inches.
Left anterior superior iliac spine to tip of left inner malleolus	14½ „
Right foot, toe to heel	8 „
Left „ „ „	7½ „
Circumference of pelvis	25¼ „
Right anterior superior iliac spine to right pubic spine	6 „
Left anterior superior iliac spine to left pubic spine	5 „
Right anterior superior iliac spine to left anterior superior iliac spine	8 „
Length of vertebral column	18 „
Length of head from occiput to root of nose	21 „
Length of humeri	9 „
Length of forearms	8 „

The patient was again admitted into the Royal Portsmouth Hospital on May 3rd, 1904, suffering from advanced phthisis and died from exhaustion on June 18th.

Autopsy: right leg.—Articulation, a projecting nodule of bone, the size of the last joint of a large thumb, attached to the pelvis, on and below the anterior border of the innominate bone, and in a situation corresponding with the anterior inferior spine of the ilium. There is no trace of an acetabulum. Above and to the outer side of the thyroid foramen is a large smooth surface over which the bone referred to has glided.

Left leg.—About three inches from the anterior superior spine of the ilium is a projecting osseous element, against the lower end of which the head of the tibia articulated. The left side of

the pelvis is more developed than the right. The upper end of this projecting element is 3 inches from the anterior superior

FIG. 56.

From a photograph of the patient when 10 years of age.

spine as against 1½ inches in the right limb, and is placed below the anterior inferior spine of the ilium. There is the same absence of an acetabulum. The articulating surface on the

pelvis is smaller on this side than on the right, and is outside the thyroid foramen. On the inner and lower surface of the upper articular end of the bone (ill-developed femur) a somewhat oval-shaped sesamoid bone, $1\frac{3}{8}$ inches in chief diameter, articulated.

The limbs were sent to the Royal College of Surgeons. I am indebted to Mr. S. G. Shattock for the following description from the catalogue of the Museum:

"The bones of the lower extremities of a man, aged 30 years, showing an asymmetrical congenital malformation. In the *left* extremity the tibia and fibula are of the full length, and present no marked abnormality, except that both are slightly curved forwards, and that the head of the tibia is unnaturally flat from before backwards. Articulating with the head of the tibia is an osseous element, $3\frac{1}{2}$ inches in extreme length, which represents an ill-developed femur. The bone itself is of somewhat triangular shape, and presents inferiorly two condyles separated by an intercondylar notch, though the projecting posterior portions of the condyles are scarcely represented.

"The femoral condyles articulate with the upper surface of the head of the tibia; there is no patellar facette in the normal position.

"The summit of the rudimentary femur presents a smooth, oval surface, with slightly overhanging borders, with which a further osseous element articulates. The latter, which, from its size and general form, may be viewed as a displaced patella, measures about $1\frac{1}{4}$ inches in its longer diameter, is somewhat pyramidal, and at its base is smoothly covered with cartilage.

"On the *right* side, the skeleton of the limb is considerably more misshapen, and much the shorter of the two, measuring in the straight line only 13 as compared with 18 inches. As on the left side, the foot was normal, except that here, as on the right, the bases of the 4th and 5th metatarsal bones were fused.

"The fibula is but $5\frac{1}{2}$ inches in length, and, except for its lower end, is uniformly diminutive; the lower end has its normal relations, and is of full size, the upper end does not articulate with the tibia.

"The shaft of the tibia, a short distance from its lower end, expands into a broad triangular process, each of the upper angles of which is enlarged in a manner suggestive of an

FIG. 57.

Photograph of the bones of the lower limbs of the patient described in the text.

articular extremity. The outer of these, which lies about 3 inches above the unattached upper end of the fibula, probably represents a greatly flattened head, whilst the inner is possibly an outgrowth of bone into the adductor muscles.

"The upper border of the triangular expansion is concave and bridged across by a ligamentous structure, with which an undersized patella is connected."

Mr. T. W. P. Lawrence has pointed out that a remarkably similar case is recorded, with illustrations, by Professor George Viner Ellis in the 'Medico-Chirurgical Transactions,' vol. xxxvi, 1853, p. 339. The individual was 55 years of age, and particularly active, having been in the habit of appearing on the stage in the guise of imps and monkeys. The deformities were limited to the lower limbs. The muscles and vessels were carefully dissected, but it may be sufficient for the present purpose to notice the condition of the bones of the lower limbs. In each innominate bone the acetabulum was wanting, its place being represented by a small depression rather less than half an inch in diameter. In each bone the anterior inferior spine was widened, and smooth for articulation with one or two small irregular pieces of bone to which the flexor muscles were attached.

No femur existed in the right limb, and only a fragment of the lower end of that bone, measuring two inches in depth and three in width, was present in the left. The right tibia was widely forked above, and each point was attached by muscle and ligament to the pelvis, but without any articulation or even contact; the outer point, which was the continuation of the shaft of the bone, was ankylosed with the head of the fibula.

The tibia and fibula of the left leg were nearly of the usual size, but were slightly deformed above and rather bent in their shafts.

There was no hip-joint on either side, the connection between the bones of the limbs and the pelvic arch being effected by muscle and ligament, but without contact. In the right limb the two branches of the tibia were directed upwards towards the pelvis, the first being near the front of the pubes, the other behind the front of the innominate bone, and they were fixed in these positions by fibrous bands and muscles, whilst at the midpoint of the fork the bone was further united to the pelvis by

other ligamentous bands. In the left limb the remnant of the femur projected upwards amongst the muscles and was connected by ligamentous structures to the front of the innominate bone; on the left side the knee-joint was nearly complete. The adductors of the right limb, only two inches in length, were attached to the inner point of the tibia.

The skeleton of this individual is preserved in the museum of University College, London. *May 16th*, 1905.

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32. *On secondary carcinomatosis of bones and osteoplastic changes connected with them.*

By F. H. THIELE.

THE reason for bringing forward this condition is that several cases of extensive secondary carcinomatosis of bones have lately come under my notice showing marked osteoplastic changes, and one case which I propose to describe in detail fully confirms the conclusions put forward by v. Recklinghausen in his monograph on the subject in Virchow's 'Festschrift' of 1891.

The case in which this extensive carcinomatosis of the bones occurred was lately in University College Hospital. The condition was secondary to carcinoma of the prostate, which had caused no symptoms. The patient was 71 years old, and was admitted to the hospital for painful swellings on his ribs and pain in the legs. He noticed the swellings over the ribs for at least two years before admission to the hospital. At the autopsy it was found that the prostate was moderately enlarged and uniformly infiltrated by a firm, whitish mass of growth. The prostatic urethra was distorted by the growth, which did not extend beyond the prostate. There were a few nodules of growth in the bladder involving the mucous membrane. The pelvic glands were infiltrated with growth, but beyond these and the extensive deposits in the bones there were only a few nodules of growth in the pleura and in one bronchial tube.

Deposits of growth occurred in the vertebræ, pelvis, scapulæ, ribs, bones of the limbs, and sternum.

In the sternum there was a large mass of growth projecting on either surface of the manubrium. The growth was not

adherent to the subcutaneous tissues, which could be easily dissected off. Nowhere could a needle be passed through the growth through the bone. There were no bony structures in the growth outside the manubrium. A few small growths were present at the sides of the sternum, and a larger one occurred on the posterior surface of the xiphisternum. When the sternum was cut through longitudinally it was found to be very dense, there was no distinction between the compact and cancellous bone, and no red marrow could be seen. The bone was composed of thick, white, closely meshed trabeculæ with white strands of growth in the meshes.

The ribs on both sides were equally affected, being practically encased in malignant growth. The growth only occurred beneath the periosteum of the ribs; it nowhere extended beneath the perichondrium. The first four ribs were covered with growth in their whole extent, the last five were similarly affected, but the remaining three were free from growth on the more lateral aspect of the bone. The periosteum could be seen covering the growth in many places, but in others large prominent masses occurred, which grew in between the bundles of the muscles. On the pleural aspect the pleura could easily be pulled off the growth.

On section the ribs were very dense, they were only slightly expanded. The cancellous tissue was entirely obliterated; the rib was one uniform mass of closely meshed, thick, trabeculæ of bone. There was no bone in the growth outside the ribs. The bone was so hard that it took a considerable time to decalcify it even by the rapid method of nitric acid in formalin.

Both scapulæ were affected by growth, the right more than the left.

On the right side the infraspinous fossa, at its central part and immediately below the spine, was free from growth. There was a thick mass of growth at the inferior angle extending up along the axillary border to a large mass of growth around the glenoid cavity. There were only small, flat growths along the vertebral border.

The under surface of the spine of the scapula had a fairly thick mass of growth on it, ending just before the neck of the acromion process.

The acromion had a large mass of growth on its upper surface

near its outer edge. There was also some growth near its tip on the under surface.

There was a large mass on the under surface of the coracoid process; its upper surface was comparatively free, except for a small nodule near its middle.

The growth was very thick around the glenoid cavity, especially so at the inferior and inferior lateral parts.

The suprascapular fossa was occupied by a large mass of growth, which was thickest near the superior angle of the scapula and near the root of the acromion process.

In the subscapular fossa the thinned part of the bone was free from growth. The growth was most marked at the inferior angle, around the glenoid cavity and root of the coracoid process, and in the depression corresponding to the insertion of the spine. There was very little growth along the vertebral border.

In the smaller masses the periosteum could be made out; in the larger the growth had penetrated between the bundles of muscular fibres.

There were small flat masses along the front of the vertebræ, especially laterally. These were beneath the anterior common ligament.

On the alæ of the sacrum there were flat masses of growth.

In the pelvis there was a prominent tumour on the right side projecting from the region of the base of the ischial spine and great sacro-sciatic notch. A smaller flat mass could be made out on the opposite side in a corresponding position.

There were no other masses on the true pelvis.

In the iliac fossæ the central parts were free from growth, but there were masses beneath the muscle at the posterior part of the iliac fossa and near the anterior iliac spines, reaching on the right side to the edge of the acetabulum. The outer side of the innominate bone showed a mass of growth around the acetabulum extending upwards beneath the gluteus minimus. The posterior part of the iliac bone was not examined.

There were osteoplastic growths in the heads and necks of both femora; the bones had the same white opaque appearance as the sternum, and on the right side the growth had spread to the surface beneath the synovial membrane and the synovial sacs of the glutei. On the left there were less marked subperiosteal growths.

In the heads of the humeri there were also deposits of new-

growth, with bony changes, as in the femora. On the right side the growth had grown to the surface and formed a large mass below the head of the bone on its posterior and inner aspect.

There were no growths on the flat bones of the skull and only a few flat growths on the vertebræ towards the spinal canal. The other bones were not examined.

As will be seen from the above description, the deposits were very extensive, and their distribution supports v. Recklinghausen's view that the primary deposit occurs in the marrow and that the subperiosteal growths are secondary to this and occur through the foramina of the bones. If, now, the bones be examined with this view, it will be evident that the growths are largest and occur most where the foramina are most marked.

If we deal with the scapula first, it will be seen that in the subscapular fossa the foramina are most marked at the inferior angle, and that there are numerous and large foramina in the part corresponding to the insertion of the spine of the scapula.

In the supraspinous fossa the foramina are most marked near the root of the acromion and the vertebral end of the spine.

In the infraspinous fossa the foramina are most marked at the inferior angle. They are also very marked around the glenoid cavity, especially at its lower part, on the under surface of the coracoid and posterior surface of its root. On the acromion they are most marked on its upper surface, and on the lower at its tip. On comparing this with the distribution of the growth it will be seen that the two correspond very closely indeed. The places where the bone is thinnest and smoothest were free from growth.

In the ribs there is no such marked grouping of foramina, but on examination it is seen that there are large groups of small foramina towards the anterior extremities and the angles of the ribs on the outer surfaces, the lateral parts being free from orifices of any size.

On the inner surface the foramina are fairly uniformly distributed along the groove for the vessels. The distribution of the growths corresponds again to this arrangement; the lateral aspects of the ribs are free or the growth is least marked there.

In the upper extremity of the humerus the most marked foramina are near the great tuberosity in front, and behind in a triangular area below the articular surface of the head. This also agrees with the distribution of the growth.

In the pelvis the most marked foramina occur at the posterior and upper part of the iliac bones, the region of the anterior spines of the ilium, and in the true pelvis they are most developed around the base of the ischial spine and adjoining bone bounding the great sacro-sciatic notch.

This case agrees with v. Recklinghausen's formula for the distribution of the subperiosteal growths; the central parts of the iliac bones, which are thinnest and smoothest, are free from growth, the basin-like form of the iliac fossa being increased by a ring of growth around this. The inner surface of the bones forming the true pelvis is hard and smooth; the only large foramina are near the ischial spine, and it is here, according to v. Recklinghausen's theory, that the growths should develop, as has occurred in some cases quoted by him and in this case.

On the outer aspect the bone is roughest around the upper and posterior parts of the prominence of the acetabular wall, and the aspects of the rami of the pubis and ischium turned towards the obturator foramen.

The other parts, with the tip of the ischial tuberosity, are smooth. The outer surface of the iliac bone has the foramina most marked near the posterior part of the bone some distance from the edge.

According to the theory, therefore, the growths should occur most markedly around the acetabulum and the other rough parts, and this is fulfilled by the positions of the growths here seen.

In the upper extremity of the femur the foramina are largest and most numerous along the surgical and anatomical necks of the bone and the front of the great trochanter. The subperiosteal growths, here again, are most marked in these regions, growing beneath the synovial membrane.

In the spinal column the foramina are very numerous in the bodies of the vertebræ, whereas the laminæ are composed of denser and smoother bone, and corresponding to this, subperiosteal growths are rare or only feebly marked on the laminæ. The alar masses of the sacrum are also very porous, and so growths can easily occur here.

It will, therefore, at once be evident, from a comparison of the localisation of these subperiosteal carcinomatous deposits and the grouping of the large foramina in the bones for the passage of the vessels, that these subperiosteal carcinomata are

due to the extension of intra-medullary deposits through these foramina to the subperiosteal tissues, and are not primarily subperiosteal. Also the position of these growths bears no relation, as was demonstrated by v. Recklinghausen, to the insertions of powerful muscles. These subperiosteal growths are not due to the extension of an intra-medullary deposit into the subperiosteal tissues from erosion of the bone in front of the growth, as is evident from this case where the bone maintained its shape and was nowhere eroded.

v. Recklinghausen showed that the bone metastases occur in the vascular channels of the marrow and that the deposit first takes place there, not necessarily by a mass large enough to block the channel, but by the stagnation of even isolated malignant cells in the periaxial stream in the medullary sinuses and their multiplication there. The vascular channels of the bones are relatively wide and are of a fixed calibre, and so do not undergo variations in size in correspondence with variations of the channels leading to them. Hence when the extra-osseous channel becomes narrower as the result of peripheral stimulation the blood from them runs into a relatively much wider channel, the periaxial stream becomes slower, stagnates, forms eddies, and if malignant cells are present in the blood, they accumulate in this stagnating periaxial channel and multiply in the highly nutritive pabulum there, become adherent to the wall, and finally fill the channel.

This conclusion is strengthened by the observations of Bizzozero and Denys, who state that the leucocytes accumulate in the parietal parts of the marrow capillaries and undergo active multiplication there.

The lymphatic glands similarly favour the settling of malignant cells, for here again there are relatively wide irregular channels with a slow stream.

Hence, according to v. Recklinghausen, when malignant cells are circulating in the blood, the greatest number of metastases should occur in the bones, and in those bones which are subject to the greatest amount of strain and to the most frequent variations in temperature. He puts the order of involvement of bones from metastasis due to prostatic carcinoma as vertebræ, femora, pelvis, ribs, sternum, humerus, flat bones of the skull, fibula, tibia, radius, and ulna.

The three chief sources of secondary carcinomatous deposits in bones are primary carcinoma of the prostate, thyroid, and mammary glands. Bone metastases have also been seen where the primary focus has been in the stomach, uterus, and œsophagus.

There does not appear to be any difference in the distribution of these bone metastases, whether the primary focus be mammary, thyroid, or prostatic. v. Recklinghausen showed that the order of frequency of affection of the various bones was about the same wherever the primary focus. Thus in cases of mammary carcinoma the order of frequency is the spinal column, the ribs, sternum, femora, humeri; the affection of the pelvis is uncertain. Again, he endeavoured to show that in the distribution of the secondary deposits in bone in cases of melanotic sarcoma the same order of frequency of affection was observed, viz., vertebræ, bones of trunk, proximal ends of limb bones, the skull. It would thus appear that the order of frequency of affection by metastases was the same whether the growth be primary in the prostate, breast, or thyroid, or whether the growth be sarcoma or carcinoma.

The frequency of bone metastases in cases of prostatic carcinoma varies considerably according to various estimates. Wolff, 1899, gives it as 13 per cent.; Kaufmann, 1902, places it as 34 per cent. These are from all available statistics, cases where careful examination was made for secondary deposits or not. Kaufmann found bone metastases in 16 out of 22 carefully examined cases.

According to Limbacher, bone metastases occur in 37 per cent. of cases of thyroid cancer; and in 14 per cent. of mammary, according to Linzinger. These figures, of course, are very inaccurate owing to the frequent incomplete examination of the bones at autopsies, since the deposits in bone are rarely productive of any great destruction of the bones or any prominent tumours. v. Eiselberg's view as to the mode of transmission of thyroid carcinoma has been accepted for prostatic growths as well. v. Recklinghausen pointed out that tumours of the prostate readily got into the blood-vessels and spread in this way. Cohnheim made similar observations on tumours of the thyroid, and later Winniwarter made the observation that thyroid cancers break directly into veins more commonly than any other. The

thesis, as regards the prostate, possesses probability since phleboliths are common in the prostatic veins. In other carcinomata the dissemination takes place through the lymphatics into the vascular channels or by ulceration directly into veins. In all cases, however, the cells must be carried through the capillaries of the lungs and heart before reaching the bones, and it is peculiar, especially in cases of prostatic carcinoma, that so few secondary deposits occur in the lungs.

In the case recorded above there were a few nodules in the pleura and one in a bronchial tube. In another case, lately in University College Hospital, of prostatic carcinoma there were a few secondary deposits in the vertebræ and ribs, with a few nodules in the lungs. The lung metastases in both cases were very few as compared with the bone metastases. Such instances are not, however, limited to prostatic cases, since in a case of epithelioma of the œsophagus lately observed there were metastases in bone without any deposits in the lungs at all.

Various theories have been advanced to account for this skipping of the lungs and the predominance of the skeletal metastases. Thus Neusser advocates a theory based on the assumption of a blood relationship between the mammæ, thyroid, prostate, and bone-marrow. This blood relationship cannot be advanced for the œsophagus and bone-marrow.

The more probable theory is that of v. Recklinghausen that the capillary channels of the marrow are relatively much wider, and so a slower circulation occurs in them with greater slowing of the periaxial stream, with consequent accumulation and multiplication of any malignant cells that may be in the blood. This is further aided by the temporary greater discrepancy in relative calibre between the extra and intra-osseous channels whereby periodically the periaxial stream is rendered still slower.

v. Recklinghausen further drew attention to the marked osteoplastic changes that occur in connection with secondary carcinomatous deposits in bones, especially with carcinoma of the prostate. He further maintained that the change could also occur with bone metastases from other primary sources. The osteoplastic change occurs not only in the intra-medullary deposits but also in the subperiosteal outgrowths from these, leading to the production of peculiar tumours with plates and spicules of

new bone, so that in macerated specimens spongy exostotic tumours are seen, and v. Recklinghausen thus explained the occurrence and mode of formation of peculiar spongy exostoses in a museum specimen he found at Strasburg. He states that this bony change occurs, not only about scattered carcinomatous areas as evidences of reactive irritation at the borders of the growth formed by the old tissue in the manner of an inflammatory proliferation set up by the growth, but also as an integral part of the tumour in the bone even though it is a carcinoma.

The evidence of the new bony formation is given by—

(α) The regular occurrence of a nucleus of spongy bone even in the youngest medullary growths.

(β) The great sclerosis, amounting to almost complete eburnation of the bones, as may be seen in the neck of the femur, etc.

(γ) The sclerosis which occurs so markedly in the vertebræ and ribs.

(δ) The alteration in the arrangement of the trabeculæ of the bone.

(ε) The presence of spicules and plates of bone in the subperiosteal growths.

The osteoplastic change is not ascribed by v. Recklinghausen to any inherent peculiarity in the nature of the growth, but is simply an accidental local attribute due to the new soil into which it has been transplanted, and not a peculiar or general property of this variety of carcinoma.

He further stated that the change occurs in the bone metastases of primary carcinoma of the breast. The occurrence of these osteoplastic changes appears to depend on the way the focus grows. If it be of an infiltrating character, as usually occurs in carcinoma of the prostate, the bony changes take place; if the growth be sharply defined, then not. So that when the deposit in cases of mammary carcinoma is infiltrating, osteoplastic changes occur in it. v. Recklinghausen puts the cause of these osteoplastic changes to chronic venous congestion of the affected part. The multiplication of malignant cells in the medullary capillaries leads to thromboses of these, with infarction and chronic venous congestion.

I have lately had the opportunity of examining several small medullary growths, and have been able to confirm this statement,

viz. that a small infarcted area frequently occurs in these bones, with chronic venous congestion and osteoplastic changes in this congested part.

Osteoplastic changes occur in other conditions in which there is chronic venous congestion. Thus it has been shown that a larger bony callus is produced in a broken bone if the limb in which the fracture has occurred be rendered passively hyperæmic. Bamberger has shown that in the chronic venous congestion which occurs with chronic pulmonary disease not only does clubbing of the fingers occur, but the distal parts of the phalanges show osteoplastic periostitis, and even the trabeculæ of the spongy bone become increased in calibre.

This osteoplastic change also occurred in the two cases of carcinoma of the prostate examined by me. In the case with the extensive subperiosteal growths the osteoplastic change had only occurred in the part of the growth in the bone; there was no bony change in the subperiosteal tumours. There were marked osteoplastic changes in the necks of the femora, in the ribs, sternum, vertebræ, and scapula. The ribs and sternum were dense, almost like ivory; the great bony change was well brought out by the radiographs taken. Microscopically the decalcified bone consists of thick trabeculæ of bone with rather large lacunar spaces. The lamellæ of the bone are arranged concentrically to the growth in the meshes. The growth has no connective-tissue stroma; it consists wholly of epithelial-like cells; the malignant cells are in direct contact with the new bone.

In the other case there were deposits in the vertebræ and ribs. The growths in the vertebræ had not undergone any osteoplastic process; in the ribs, however, which were slightly expanded, marked osteoplastic process had occurred, and in places there were small nodules of bone of almost ivory density lying in the more cancellous bone.

All growths in bone secondary to carcinoma of the prostate do not apparently undergo osteoplastic processes. The case recorded by Sir Henry Thompson in the 'Transactions' of this Society brings this point out. There were soft encephaloid growths in the lower dorsal vertebræ; the growths were not infiltrating in character.

These cases, therefore, show:

(1) That metastatic growths occur primarily in the medulla of bones.

(2) That they spread to the subperiosteal tissues through the foramina and so occur where the bone is roughest and most porous.

(3) The growths occur especially in those bones which are most liable to strain, injury, and variations in temperature.

(4) The growths frequently show osteoplastic changes. The more infiltrating the deposit is the greater tendency there is to these osteoplastic changes.

(5) These osteoplastic changes occur not only in deposits from carcinoma of the prostate, but also with carcinomata when the primary focus is elsewhere.

From an analysis of the changes produced in bones by metastases in them the following classification can be made:

(1) Simple erosion of the bone by the growth, without any marked expansion or osteoplastic process.

(2) Great expansion of the bone, osteoplastic processes marked in the bone.

(3) Infiltration of the bone without marked expansion, but with osteoplastic changes.

(4) Extension of the growth to the subperiosteal tissues, with or without osteoplastic changes in the subperiosteal growth.

The question then arises as to the difference in the causation of these. Does it depend on the nature of the growth or the rate of growth and mode of growth? It does not apparently depend on the nature of the growth, since not every metastasis from carcinoma of the prostate shows osteoplastic changes, not even in different metastases in the same patient, and again, osteoplastic processes may occur in bone metastases from carcinoma primary in the breast. Again, in the same patient in one place the metastases may simply erode all before them, in others produce expansion with osteoplastic changes; such cases I have lately observed in a case of epithelioma of the œsophagus with growths in the ribs causing expansion, and in the sternum and vertebræ causing simply erosion. Again, in a patient with carcinoma of the breast a secondary deposit on one radius caused expansion, on the other side the radius was not expanded but fractured.

It would therefore appear that the more slowly growing the metastasis and primary growth are, the more infiltrating and less

sharply defined the metastasis is, the greater is the tendency for osteoplastic changes. Very rapid growths appear to produce simply erosion, less rapid produce expansion as well.

This appears to be corroborated from the evidence; carcinomata of the prostate are usually very slow growing and their metastases are also very slow in growth and may apparently produce noticeable tumours for several years before the fatal ending; microscopically they are of an infiltrating character and show marked osteoplastic changes.

In the rapidly growing and sharply defined metastasis, as with carcinoma of the breast, the osteoplastic change is very slight and erosion chiefly occurs.

I should further like to draw attention to a peculiar change which I have observed in sections of a rib which was expanded from the growth of a metastasis in a case of epithelioma of the œsophagus. The specimen came from a man, aged 38 years; the growth in the œsophagus was small, there was extensive infiltration of the chest and abdominal glands by growths; there were deposits in the vertebræ, sternum, and ribs; there were no signs of joint affection.

The rib examined had in it, in its mid-axillary line, a fusiform swelling an inch thick. Nowhere was there any fracture. The rib on section showed small nodules of cartilage to the naked eye. On microscopic examination it was seen that there were marked osteoplastic changes all around the periphery of the bone, and in this newly-formed bone were numerous areas of cartilage. In these areas were typical cartilage cells; the stroma in some parts was homogeneous, in others fibrillated and the fibrillæ were continuous with fibrillæ in the newly-formed bone. In some places calcification of the cartilage had occurred. The cartilage passed directly into the bone, the cartilage cells presenting all stages of transition, from cartilage cells to lacunar cells. The rest of the section showed infiltration by growth, and the cells in many places had lost their typical epithelial structure and become greatly elongated. In most places there was a fibrous-looking stroma between the malignant cells and bone cancelli; in others the cells were in direct contact with the cancelli. There was new bone-formation in the growth.

A similar change was observed in the vertebræ. Cone, in a report of a case of metastases in bone from a case of carcinoma of

the prostate, mentions a cartilaginous nodule in a mass of growth in the ilium. This cartilaginous nodule was in the midst of denser new bone-formations.

The origin of this cartilage may be due to small fractures in

FIG. 58.

Section of part of a rib expanded by a metastasis from an epithelioma of the œsophagus. The right side of the figure shows infiltration by the growth. The metastasis has lost a great deal of its epithelial character; there are a few cell-nests and typical epithelial cells, but many have become more spindle-shaped. On the left hand side there are large cartilaginous trabeculæ. The cartilage at its upper part is clear and homogeneous; at its lower it shows calcification. Along its right edge it is fibrillar, the fibrillæ being continuous with those of the (artificially) decalcified bone and also with bone newly-formed. The position of the metastases was in the mid-axillary line.

the bone due to the expansion and the consequent production of callus-containing cartilage, as was suggested by Mr. Shattock, to whom I showed the specimen.

In conclusion, I have to thank the staff of University College Hospital and Mr. Lawrence, the Curator of the Museum of University College, for placing the material at my disposal.

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1905.

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33. *A case of squamous-celled carcinoma of the finger, associated with frequent and prolonged exposure to X rays.*

By ALEXANDER G. R. FOULERTON.

THE sections shown this evening are from a case of squamous-celled carcinoma of the finger occurring in a surgeon whose hands had been subjected to almost daily exposure to X rays for a period of some seven years.

The history of the case is as follows: C. R. C. L—, aged 46 years, first began to work systematically with X rays in 1897, and since then has been exposed to their influence day by day with short intervals of vacation.

In 1899 he first noticed some loss of tactile sensation in the

fingers of both hands; at the same time the skin of the dorsum of the hands became dry and scaly and the hair fell out, the nails also became hard and brittle.

In May, 1903, a severe attack of dermatitis followed the performance of a long operation during which the left hand especially was closely exposed to the rays; the skin of the dorsal aspect of the index, second, and third fingers was most seriously affected, being severely blistered. The resulting ulcers on these fingers were four months in healing over, and the new skin was thin, showed numerous nævoid-looking petechiæ, and remained tender for some time. The nails fell out, and the new ones replacing them were irregular and grew slowly. Warty patches developed on the skin of the dorsal aspect of the middle phalanges of the index and second fingers.

A second attack of dermatitis followed another unusually prolonged single exposure to the rays in December, 1903. The skin of the dorsal aspect of the index and second fingers of the left hand was again blistered, and a small ulcer over the middle phalanx of each finger again resulted.

The ulcer on the second finger healed up, but that on the index finger remained open and became the seat of severe pain, which was especially accentuated at night-time.

In February, 1904, the ulcer of the index finger was treated with a saturated solution of potassium permanganate. The application was followed by some improvement, and up to April indications of healing were noticed. All attempts at healing then ceased, and between May and September the ulcer gradually increased in superficial area and in depth.

In September, 1904, the ulcer then having a superficial area measuring about $\frac{1}{4} \times \frac{1}{2}$ inch, the finger was amputated at the metatarso-phalangeal joint.

At the present time there is a small superficial ulcer with a dry, scabbed surface on the back of the middle phalanx of the second finger of the left hand. The skin of the dorsum of both hands is thin, and of shiny appearance; the nails of both hands are thickened and irregular; nævoid-looking petechiæ are scattered thickly over the dorsum.

At the present time, eight months after amputation of the finger, there is no indication of any secondary development of the disease.

Histological appearances of the new growth in the index finger. In a section made vertically through the skin and parallel with the long axis of the finger the following appearances are seen. At the distance of 0·8 centimetre or less from the margin of the ulcer the skin is of normal appearance, except that the stratum corneum is perhaps unusually thick. The corium shows the normal papillary structure, and here and there are small areas of round-celled infiltration immediately below the epidermal cells. As one approaches nearer to the margin of the ulcer the entire thickness of the epidermis is increased and the papillæ of the corium become fewer, or are absent; but there is no definite downgrowth of the epithelium. At the very margin of the ulcer the epidermis, still with a well-defined basement line, dips down to the ulcerated surface. From the margin of the ulcer the epithelial cells can be seen growing freely outwards into the substance of the corium and underlying tissue, between the thickened epidermis above and the bone below; at one point, at any rate, the underlying bone has been invaded by the new growth. Cell-nest formation is very frequent and conspicuous; and in a large majority of instances the cell-nests have undergone a complete keratinisation, the appearance presented being such as one usually associates with very chronic types of squamous-celled carcinoma.

The exact significance of this, the third case of squamous-celled carcinoma of the hand which has occurred amongst the comparatively small number of those who are specially engaged in X-ray work in London, is not quite clear. I think it is certain that the malignant overgrowth of epithelium is not due to any specific stimulating action on the epithelium of the X rays themselves. All the available evidence points in the opposite direction, and suggests rather that any specific action of the rays is inhibitory of epithelial growth; and, moreover, except in the immediate neighbourhood of the ulcer, there is no sign of any special activity of the epithelium.

On the whole, it seems probable that the case is merely an example of malignant epithelial overgrowth, starting from a chronic ulcer, such as frequently occurs elsewhere. And one must suppose that the special liability of such chronic ulcers when occurring on the hands of those who are constantly exposed to the local influence of X rays is due to continuous irritation

caused by their application, of which irritation acute dermatitis is the most obvious result.

The appearances in this case suggest that even when the malignant new growth has started, an inhibitory action of the rays may still exert some influence on the epithelial cells which are growing out from the ulcerated surface. *May 2nd*, 1905.

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34. *Broncho-pneumonia with multiple cavities.*

By JULIUS M. BERNSTEIN.

A FEMALE child, aged 3 years, was admitted to the Westminster Hospital under Dr. de Havilland Hall, to whom I am indebted for permission to publish this case. Until three months previously she had not suffered from any serious illness. There was a history of pain in the back for three months and cough for one month.

On admission the lips were blue, the alæ nasi working, pulse 148, respirations 76, and there were numerous fine râles all over the chest. She remained cyanosed for three days, with a temperature of 102°; then the respirations became embarrassed, vomiting set in and death ensued. At the *post-mortem* examination, made fifteen hours after death, the body weighed 22 lb., and measured 31 inches in length. The chest was barrel-shaped, and the diaphragm was pushed downwards on the right side, so as to be convex towards the abdomen. This was due to a pneumothorax on the right side, the air hissing out on puncturing the chest. The right lung was somewhat retracted. Both lungs were of a bluish tinge, and the entire surface appeared blistered owing to the presence of closely-set bullæ varying in size from a pin's head to about $\frac{3}{8}$ inch in diameter, which resulted in a peculiar mottled appearance. On section the lung tissue was seen to be honeycombed by a series of cavities separated by small areas of apparently normal lung tissue, reddish in colour. These cavities were generally empty, and to the naked eye their internal wall looked white and shiny. There was little evidence of consolidation; the bronchi exuded muco-pus on pressure; the glands were not markedly enlarged, and there was nothing

pressing on the bronchi or trachea. The pleuræ were fairly smooth and shiny. The liver weighed 17 oz. and was pushed down below the costal margin by the pneumothorax. On section it showed a few small yellowish nodules, about the size of a pin's head or slightly larger, situated in the portal canals; otherwise it appeared normal. The remaining viscera showed nothing abnormal. Heart weighed 2 oz., spleen 1½ oz., kidneys 2 oz. each. Microscopically in the lungs there is evidence of an ex-

FIG. 59.

A section of the lung, slightly enlarged, showing the cystic condition described in the text.

tensive broncho-pneumonia. The more normal bronchioles are filled with cell-exudation and exfoliated mucosa, and surrounded by a peribronchitis. In these parts the alveoli are choked with small round and endothelial cells, but no fibrin, and the blood-vessels are engorged. In places the tissue is distinctly emphysematous. The cavities in most cases show no lining membrane, but are surrounded by an accumulation of closely packed round to oval cells. In a few of the smaller ones, however, there is a well-marked columnar epithelium, resembling the bronchial mucosa, and more or less stretched according to the size of the cavity. Some are irregular in shape and appear to represent

a terminal bronchiole, dilated, and lined by epithelium, and continuous with a dilated infundibulum, surrounded by cellular exudation (microphotograph).

A marked feature is the presence of giant cells in the walls of some of the cavities and in places in the centre of a mass of cell-exudation. But neither the cell-exudation nor the rather small-sized giant cells present the appearances met with in typical tuberculous consolidation.

Numerous sections stained with Loeffler's methylene blue, Gram's method, and Ziehl-Neelsen stain failed to demonstrate any micro-organisms.

The liver nodules consisted of infiltrations of small round and oval cells, apparently surrounding the bile-ducts (pericholangitis). In the larger areas of infiltration there was central degeneration and the presence of bile-pigments. Here also no micro-organisms were demonstrated.

At first sight it seemed possible that a gas-forming organism was the cause of the cavitation, but the absence of any micro-organisms whatsoever rendered this unfeasible. Neither was there any evidence to support the view that it was due to breaking down abscesses, and against this also is the epithelial lining of some of the cavities, and the more or less stretched epithelium of some of the larger cavities. The pneumothorax pointed to a direct communication between the bullæ and the air-tubes, and this is supported by certain microscopical appearances. Probably the coughing led to rupture of some of the bullæ, and hence to the escape of air into the thorax. In a similar case described by Sharkey there was extensive subcutaneous emphysema of the body and arms.

In a case brought by Tooth before this Society the Morbid Growths Committee decided that tuberculosis could not be excluded in the absence of inoculation experiments, and giant cells were also present.

In the case now described the presence of numerous giant cells suggested the possibility of a tuberculous origin, notwithstanding that the histological appearances were not those characteristic of tuberculosis, which fact was further supported by the failure to detect any bacilli after very careful investigation. Moreover, too much stress must not be laid on the presence of giant cells in broncho-pneumonia, as we have found

at Westminster Hospital that their presence is by no means infrequent in this disease when tuberculosis can be definitely excluded. In a similar case described by Morley Fletcher there was acute bronchitis and peribronchitis, and acute bronchiolectasis associated with a pericholangitis; the absence of pneumonic consolidation was especially noted.

In the three cases quoted (all of which occurred in young children previously healthy and with an acute history) there was a general opinion that the cavities were bronchiolectases. In the case here described the sequence of events seems to have been: acute bronchitis and bronchiolitis, peribronchitis, bronchopneumonia, ending in dilatation of the terminal bronchioles and the infundibula. But the mechanism of the dilatation is less definite. R. G. Hebb suggests that, in the absence of a gas-forming organism and the want of evidence that the cavities are due to breaking-down abscesses, the condition might be due to the valve-like action of the bronchiolar secretion, assisted by the peribronchial exudation constricting or rendering rigid the finer tubes at certain sections, and, as in a spray bellows, allowing entry of air, but impeding exit, and so resulting in distension of the bronchioles and infundibules. The association with the pericholangitis might be merely a coincidence, but a similar condition was found in Morley Fletcher's case, and it is quite probable that both lesions may be due to an autogenetic toxin, having its primary source in the intestine, infecting the liver by direct extension along the bile-ducts, or by the portal system, and thence passing to the right heart, to be distributed to the pulmonary circulation.

May 16th, 1905.

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35. *Inquiry into the opsonic content of the blood-serum in healthy individuals and in patients affected by lupus.*

By W. Bulloch.

De opsonino in sanguinis normalis sero et in sero illorum e lupo *ægrotantium.*

Summarium.

Hæc experimenta facta sunt ut determinetur ratio, sanguinis inter opsoninum[1] et effectus qui ex Roentgen aut ex Finsen radiis oriuntur in illis e *lupo* ægrotantibus.

Indagatur serum horâ unâ aut duabus horis postquam sanguis e corpore emittitur.

Modum illum adhibui quem A. E. Wright[2] primus excogitavit.

(1) *Ægrotantis serum.*—Sanguis cujus serum indagandum in capsulo vitreo recipitur.

(2) *Sanguinis normalis leucocyti lavati.*—Ex homine sano emittitur sanguis in liquorem sodii chloridi (0·85 per cent.) in quo dissolvitur sodii citras (1 per cent.). Tunc in tubulis sanguis in turbine rotatur; corpusculorum sedimentum deinde in liquore sodii chloridi (0·85 per cent.) lavatur, et liquor supernatans defunditur.

(3) *Bacillorum tuberculosorum suspensio.*—Paratur suspensio bacillis in mortario terendis (in liquore sodii chloridi, 1 : 1000).

In tubulos capillarios trahuntur, ægrotantis seri, partes tres; suspensionis bacillorum, pars una; corpusculorum sanguinis normalis lavatorum, partes tres.

His mixtis tubuli in cistâ calefactâ (37° C.) ponuntur.

[1] Opsoninum (ὀψωνέω). Hoc nomen a A. E. Wright imponitur corporibus quibusdam in sanguinis sero, quæ corpora bacillos sic afficiunt ut leucocyti includere eos possunt.

[2] 'Proceedings of the Royal Society of London,' 1903, vol. lxxii, p. 357.

Post horæ partem quartam vacuefiunt tubuli capillarii, et mistura secundum artem histologicam examinatur. Indagantur 50 leucocyti polymorphonucleati. Computatur phagocytosis dividendo bacillorum summam summâ leucocytorum. Index opsonicus in hoc modo reperitur: dividitur numerus bacillorum tuberculosorum in leucocytibus clausorum, quum serum tentandum adsit, a numero bacillorum in leucocytibus clausorum quum adsit serum hominis sani.

Observationum tabulæ demonstrant therapeusem minime efficere quum index opsonicus certe minor quam normalis est.

Tabulæ quoque ostendere videntur radios ultraviolaceos e Finsen lucernâ emissos nihil contra bacillum ipsum efficere; quod si non esset, therapeusis in effectu constans esse debet. Utriusque modi effectus salutares forsitan causantur sanguine affluente atque telarum incitatione.

The following observations were made to determine upon a fairly large scale the opsonic content of the serum of individuals suffering from Lupus in comparison with that which obtains in individuals presumably healthy, or, at any rate, not suffering from tuberculosis. Manifestly it is a matter of importance to determine, first of all, whether there are variations in the opsonic content of the serum in healthy individuals, as the test employed at the present time necessitates the use of serum from a normal individual as a control.

The discoveries of Wright and Douglas of the opsonic content of the serum have created wide interest in clinical circles and a desire to apply these methods in medical practice. Past experience shows that disappointment may follow the precipitate anxiety on the part of the clinician, and it becomes necessary to determine on as wide a basis as possible the fundamental data which underlie the phenomena discovered by Wright, and from a practical standpoint to determine on a large number of people, healthy and diseased, the variations which may occur in the

opsonic index. It is only in this way that an opinion can be formed on the opsonic test as a diagnostic or prognostic aid. The following observations have been carried out with this aim, the number of individuals examined being 216, viz. 66 normal and 150 cases of skin tuberculosis, mostly in the form of Lupus, obtained from the Skin Department of the London Hospital. These Lupus cases constitute an important series, as they were all undergoing a system of treatment by Finsen light, and it has been possible to form some opinion of the relation of the opsonic test to the results obtained by the Finsen light. The statements made subsequently as to the cure of the particular Lupus patients was in all cases supplied to me independently by those in charge of the Finsen Therapy Department *after* I had made the opsonic determinations.

In all cases the serum was tested within an hour or two after the blood had been withdrawn from the body, and the test material employed was an emulsion of tubercle bacilli. It cannot be sufficiently emphasised that the preparation of this emulsion is of fundamental importance, and a considerable amount of care has to be taken to get it of the right density, otherwise the subsequent counting may be different and even fallacious.

Technique.—The technique employed was that of Wright and as described by him in various publications.[1] The blood was collected in a glass capsule with a recurved limb. When the blood coagulates the tube is hung in a centrifuge, which expedites the separation of the serum.

(2) The leucocytes were in all cases obtained from myself by pricking the finger and allowing the blood to run into a capsule containing sodium citrate (1 per cent.) dissolved in ·85 per cent. sodium chloride. A blood-capsule with the recurved limb bent at right angles to the plane of the body of the capsule is very suitable for this purpose, as the citrate solution can be readily run into the capsule without any risk of contamination of the solution. When the blood has entered the citrate solution the straight end of the capsule is sealed in a flame, and, when cool, the capsule is hung in the centrifuge whereby the blood-corpuscles, red and white, are carried to the bottom, sharply separated from the citrated plasma above. When the deposition of the corpuscles is complete, the capsule is cut across with a

[1] 'Proceedings of the Royal Society of London,' 1903, vol. lxxii, p. 357.

bone-pliers or file, the citrated plasma is removed by a small pipette with a teat, and the thick deposit of corpuscles is then transferred to a large 20 c.c. tube full of ·85 per cent. saline solution in order to wash the corpuscles free of traces of plasma. The corpuscles are then brought down in the centrifuge, the supernatant liquid is pipetted off, and the corpuscles are ready for use.

(3) An emulsion of tubercle bacilli is made by grinding in an agate mortar a small quantity of a bacillary mass with a solution of salt containing 1 : 1000 NaCl.

The preparation of this emulsion is a point of great importance, and great care is required in order to get it of the most suitable density. The bacilli used were those obtained on the filter-paper in the manufacture of Koch's tuberculin (T.O.). After being sufficiently rubbed up in the mortar, the bacillary emulsion is put into a tube and centrifugalised, so as to carry down the unloosened masses of bacilli, leaving above a milky emulsion of individual bacilli. If the emulsion is too thick, considerable difficulty may be experienced in subsequently counting the bacilli.

The serum, corpuscles, and bacillary emulsion having been prepared, a series of capillary pipettes are taken in hand. A mark is made on the stem of the capillary about $\frac{1}{2}$ inch from the free end, and, by means of a teat, three volumes of serum, one volume of bacillary emulsion, and three volumes of blood-corpuscles are aspirated into the stem of the pipette. This mixture should then be blown out and aspirated in, by means of the teat, several times to insure proper mixing. When this has taken place, the end of the capillary is sealed, the wide end marked with the name of the patient or the number, and the time noted. The pipette, with its contents, is then placed in the incubator at 37° C. and, after fifteen minutes, it is removed and the contents transferred to a slide on which the subsequent count is to be made. The slide is prepared by roughening its surface by fine emery-paper (No. 000) as first suggested by Wright, this method invariably giving, with the cheapest slides, excellent films without any other preparation in the way of cleaning, boiling, etc.

When the mixture of bacilli, corpuscles, and serum is placed on one end of the slide the actual film is made by spreading it out by means of a second slide. This is best done in such a way

that the second slide is applied about three quarters across the first, so that a free edge is obtained to the film. In this free edge can be obtained a large number of leucocytes, and it is the only part of the film which it is necessary to examine. The film should not be made too thin.

The film is fixed with perchloride of mercury (sat. sol.), and is then stained. Perhaps the best results are obtained by staining first of all, with Ehrlich's hæmatoxylin, washing in water hot carbol fuchsin, 2 per cent. anilin chlorhydrate, alcohol, water. The film is then dried with blotting-paper, and is ready for the determination of the ingested bacilli.

Staining with hot carbol fuchsin, subsequent decolorisation in 2 per cent. H_2SO_4, and counterstaining with Loeffler's blue, may also be used, but seems to be more uncertain in its results.

The free edge of the film is then placed under the microscope and in every polynuclear leucocyte encountered the number of bacilli is counted, noted on a sheet of paper, and, after some thirty-five to fifty leucocytes have been examined, the average number of bacilli is struck and the results compared when different sera are tested.

Determination of the opsonic content of normal individuals.—To determine the question of a variation in the opsonic index of healthy people I have examined sixty-six normal sera. Thirty-four were obtained from robust medical students at ages of 18 to 30 years. The remaining thirty-two were from nurses at the London Hospital, all of whom were presumably healthy. Up to the present we have no means of constituting the necessary standard of normality except by taking the serum of an individual presumably normal, *i.e.* an individual of sound constitution, devoid of tubercular infection and without inherited disposition to the disease. The opsonic index, it will be remembered, is obtained by dividing the number of tubercle bacilli taken up per leucocyte in the presence of any serum by the number of bacilli taken up per leucocyte in the presence of the serum of a normal individual, which latter is regarded as unity. Thus

T. B. taken up per leucocyte in the presence of a given serum = 4

" " " " " " " normal = 8

$$\frac{4 \text{ T. B.}}{8 \text{ T. B.}} = \text{opsonic index } \cdot 5.$$

The reason why the opsonic *index* is taken is that in different experiments as the emulsions of bacilli vary in density, it would be useless to give merely the *number* of bacilli engulphed. One and the same serum, tested on two different emulsions, will yield entirely different records.

Opsonic index of thirty-four medical students compared with the serum of the writer = 1·0.

1	case	= 1·2
13	„	= 1·0
6	„	= 0·98
3	„	= 0·97
2	„	= 0·96
6	„	= 0·90
2	„	= 0·85
1	„	= 0·80
34	„	Average opsonic index = 0·965.

Opsonic index of thirty-two healthy hospital nurses :

5	cases	= 1·1
13	„	= 1·0
1	„	= 0·98
2	„	= 0·97
1	„	= 0·95
6	„	= 0.90
1	„	= 0·85
3	„	= 0·80
32	„	Average opsonic index = ·969.

Taking the two series together, we get an average index of ·95 for the sixty-six people, the variations in health ranging from ·8 to 1·2.

This corresponds closely to the results obtained by R. H. Urwick in a thesis presented for the degree of M.D. Cambridge. This work, carried out at St. Mary's Hospital, showed—

8	cases	= 1
3	„	= ·94
3	„	= ·90
1	„	= ·8
2	„	= 1·1
3	„	= 1·2
20	„	Average opsonic index 1·006.

Taking the two series together, we have eighty-six healthy people with an index of 0·97. It may be assumed, therefore, that the sera of normal individuals, males or females, are almost identical, an index below ·8 being rare or pathological.

Determinations of the opsonic index of individuals suffering from Lupus.—Turning to the question of the opsonic index of individuals suffering from Lupus, I have examined, as stated above, 150 cases. In this series were cases of the mildest character up to the most severe forms, which had lasted and defied treatment for as long as forty years. Compared with the average opsonic index of ·97 obtained from normal people, the average for the 150 cases of Lupus is ·75, the cases being distributed as follows:

Opsonic Index.	Number of Cases.	Percentage.
Between ·2–·3	3	2 per cent.
„ ·3–·4	3	2 „
„ ·4–·5	21	14 „
„ ·5–·6	29	19·6 „
„ ·6–·7	33	22 „
„ ·7–·8	22	14·8 „
„ ·8–·9	18	12 „
„ ·9–1·0	7	4·6 „
„ ·1–1·4	14	9·3 „

75 per cent. of the cases are below the lowest range of normal limit, viz. ·8.

As was stated above, these patients suffering from Lupus have attended the Skin Department of the London Hospital, and especially for the purpose of X-ray or Finsen-light treatment. Data are available whereby we may compare the results obtained by these therapeutic measures with the determinations of the opsonic index. As many of the cases are still under treatment, I have tabulated only those in reference to whom an opinion may be formed. This opinion has been given by Dr. Sequeira, who has had, in connection with the Finsen therapy, an unusually large experience of Lupus. In the following tables the cases are divided into two series, viz. those with an opsonic index below ·7 and those with an index above ·9.

Cases of lupus with an opsonic index below ·7.

Patient.	Opsonic index.	Remarks.
R. Q— (6)	·44	Lupus vulgaris of nose; treatment scraping, X rays; result ?.
J. B— (20)	·40	Lupus vulgaris; father died of phthisis; Finsen therapy 4 years; slow but great improvement.
J. W— (13)	·5	Lupus 4 years, spreading in spite of X rays for 1 year.
W. K— (14)	·3	Lupus 11 years; Finsen therapy 3 years; not much improved.
L. B— (10)	·55	Lupus; great tendency to relapse after Finsen treatment.
L. H— (21)	·43	Lupus not severe; healed January, 1905.
F. H— (16)	·54	Lupus 14 years; Finsen therapy 3 years; "can just be kept under and prevented from spreading."
E. C— (18)	·5	Mother and aunt died of phthisis; lupus on right cheek 18 years; scraped 3 times; Finsen light 2 years; seems healed (December 21st, 1904).
W. P— (16)	·46	Lupus of face; cured with Finsen light.
E. A— (22)	·55	No phthisis in family; lupus for 6 years; Finsen light for 1 year; doing well.
E. N— (35)	·47	No phthisis in family; lupus 7 years; Finsen light 1 year; doing well.
S. J— (27)	·53	Phthisical family history; lupus 10 years; Finsen therapy; result, cured; relapse.
L. P— (17)	·25	Lupus 6 years; doing well under light treatment.
W. S—(22)	·45	Father and paternal uncles and 1 sister all died from phthisis; lupus 22 years; scraped 12 times; elbow excised; Finsen light 8 months; doing well.
M. B— (13)	·3	Lupus very extensive on face and nose; X rays since 1900; Finsen light; little improvement.
M. B— (41)	·48	Lupus 16 years; scraped; Koch's tuberculin; apparently healed; relapsed as bad as ever in 6 months; Finsen light 1 year; cure; relapse in 2 months.
C. G— (49)	·46	Two children died from phthisis; lupus 11 years; scraped; X rays; almost healed; recurrence; again under treatment.
J. M— (37)	·55	Phthisical family history; lupus for 14 years, very extensive; scraped 16 times; Finsen light not very successful.
B. R—	·60	No phthisis in family; lupus 8 years, very extensive; scraped several times; Finsen therapy for 2 years; nodules still remaining.
B. W— (25)	·60	No phthisical history; lupus both cheeks; cured by Finsen light in 6 months; recurrence.
A. R— (17)	·65	Lupus 13 years; Finsen light 3 years; improvement very slow.

Patient.	Opsonic index.	Remarks.
E. F— (20)	·60	Father died of phthisis; sister has phthisis; lupus of face, mouth, larynx, right arm for thirteen years; some improvement under X rays and Finsen light.
M. B—	·68	Marked phthisical history; lupus 34 years; Finsen light for 3 years; slow improvement.
W. C— (26)	·62	Lupus 22 years; Finsen therapy 2 years; slow improvement.
M. S— (16)	·66	Phthisical history; lupus 15 years; Finsen light on and off for 5 years; some nodules still present (1905).
M. C— (48)	·65	Sister had phthisis; lupus nine years on nose and face; Finsen light for 4 years; a few small spots of lupus still remain (1905).
K. W— (19)	·6	No history of phthisis; lupus 10 years on nose, palate, gums, cheeks; treated with lactic and trichloracetic acids; Finsen light since 1901; iodides; much better.
A. B— (33)	·6	No phthisis in family; lupus 19 years; scraped 19 times; cauterised about 100 times; 600 sittings Finsen light; great improvement.

Cases with an opsonic index above ·9.

Patient.	Opsonic index.	Remarks.
M. S— (19)	·9	Phthisis on paternal side; lupus 18 years; Finsen light; cured.
L. C— (29)	1·1	Lupus began in scar of ulcer from tubercular gland at age of 14; in 1905 very large lupus patch over jaw; Finsen light 6 months; nearly healed.
F. S— (33)	·9	Phthisis in family; patient had hip disease at 9; lupus for 8 years; nose severely affected; Finsen light and X rays; face excellent.
J. S— (16)	·9	No phthisis; lupus 15 years; Finsen light; cured.
B. W— (42)	·9	No phthisical history; lupus 40 years; marked improvement under Finsen light.
M. T—	·9	Lupus extensive on face; Finsen light; cured; no recurrence.
M. B— (28)	1·1	Lupus 24 years; left cheek entirely involved; Finsen light for 2 years; quite healed; scar excellent.
S. M— (19)	·89	Lupus 12 years; very severe case; much improved under Finsen light.
A. S.	1·1	Lupus 13 years; "much improvement."
T. S.	1·1	Lupus 11 years; X rays; great improvement.

Patient.	Opsonic index.	Remarks.
T. A— (27)	1·4	Lupus 22 years; very severe case; almost cured.
R. S— (25)	·92	Lupus of face and stump of thigh; "has done well."
A. J— (12)	1·4	Five uncles died of phthisis; lupus 11 years; scraped and cauterised several times; Finsen light; result almost cured.
M. H— (16)	1·0	Father and 2 sisters died of phthisis; very extensive lupus; heals very slowly under Finsen therapy.
F. H— (16)	1·0	Lupus 10 years, nose, left foot, thigh; not improving.
A. J— (25)	1·0	Lupus 17 years; Finsen light 1 year; great improvement.

An examination of these tables shows, with few exceptions, that where the opsonic index is well below the normal limit, the most approved methods of treatment by X rays or Finsen light have little power to stamp out the disease, whereas with indices in the normal limit or above it the clinical impression is that the cases do well. The method by which the exposure to light in Finsen's treatment leads to beneficial results has been the subject of much inquiry. The bactericidal action of light known since the researches of Downes and Blunt, Buchner, and others, has been assumed to be the explanation, but in the hands of Finsen's collaborators it has been found that this action, even *in vitro*, is a very superficial one. When the rays have to penetrate the skin into the living tissues the state of affairs is very different, as a large amount of the light is absorbed. As a result of experiments, both in man and in animals, Klingmüller and Halberstaedter have recently shown that the tubercle bacillus in the skin is not killed after seventy minutes' exposure to the light. Lesser and others have assumed that the healing properties of Finsen light are due to the reaction set up in the tissues by the rays. The results obtained above go to support the view that ultra-violet rays from a Finsen lamp do not exert a potent effect on the tubercle bacillus itself, otherwise it would not matter what the opsonic content of the serum was, so long as the bacilli were killed at any given spot exposed to the light. It seems not at all improbable that, in addition to the tissue reaction, an important *rôle* in the cure of Lupus by Finsen light is played by the blood "determination"—*i. e.* the congestion and exudation which occur

after exposure. If the plasma is deficient in opsonin, the result upon the tubercle bacillus would manifestly be less than where a large quantity of opsonin was present. This would also suggest that considerable benefit might be acquired even in the intractable cases by raising the opsonic index and then exposing the infected areas to light.

January 17th, 1905.

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36. *Some experiments in connection with "stimulins."*

By W. B. LEISHMAN.

De "stimulinorum" actione.

SUMMARIUM.

EXPERIMENTA mea has conclusiones indicant.

(1) Sanguinis serum ægrotantium e febre Melitensi aut e febre entericâ, et animalium serum contra hos morbos culturis vivis immunisatorum, quædam continent quæ quum sanguini normali humano adduntur, illius sanguinis leucocytorum actionem phagocyticam augent.

(2) Augetur actio phagocytica contra bacillum modo illum qui in immuniendo adhibetur.

(3) Hæc corpora temperaturam 60° C. resistunt horæ partem quartam.

(4) Probare non potui hæc corpora in sero normali aut humano aut animalium adesse.

(5) Quamvis phagocytosis aucta partim causari possit agglutininis aut "corpore immunisante" in sero, hæc corpora non esse videntur ejusdem generis ac illa in hâc dissertatione descripta.

(6) Unum ex his experimentis (No. 10) forsitan monstrat leucocytos ipsos, non bacillos, affici.

Differuntne hæc corpora ab illis a Metschnikoff "stimulinis" dictis, necne?

Auctoris illius, aliorumque (Gengou, Klemperer, Besredka) experimenta apud animalia et sine mensurâ accuratâ facta sunt. Hanc ob causam experimenta illa cum meis vix comparari possunt.

Quoad calori resistunt, corpora hæc diversa, similia sunt.

Nulla phagocytosis auctio accidere videtur quum serum normale ad sanguinem additur normalem animalium speciei alius: ex contrario apud "stimulina" a Metschnikoff indagata saepe accidit illud.

De his corporibus ut de "stimulinis" dixi, propterea quod haud certus sum ea ab corporibus illis a Metschnikoff "stimulinis" appellatis vere differre.

Pro certo leucocytos stimulari non habeo.

Ad modum explicandum quo effectus causantur, plura postulantur experimenta, antequam nomen corporibus imponere audemur.

The experiments described below were commenced with a view to determining what influence, if any, was exerted on the phagocytic power of normal leucocytes by the addition to the blood of a small quantity of immune serum. Owing to pressure of other work the experiments cover a considerable space of time and, I fear, present a somewhat disconnected appearance, but as the results appear interesting, whatever interpretation be placed upon the mechanism of the effects produced, I have thought it well to place them before you.

As to my adoption of the name "stimulins" for the substances in immune sera which bring about the increased phagocytosis seen in the experiments, I have done so for the following reasons. Metschnikoff, in his treatise on immunity, describes a series of experiments conducted by himself, Gengou, Klemperer, Besredka, and others, in which the introduction of serum, sometimes normal, sometimes immune, into the serum-sacs of

experimental animals demonstrated a greatly enhanced phagocytic activity in the leucocytes of the exudation subsequently removed from the sac for examination. To the substance which these observers conceived to be present in such sera they gave the name "*stimulines*" and to the presence of these stimulines in immune sera Metschnikoff and his school attributed an important *rôle* in the processes of both active and passive immunisation. I shall refer again to the question of the identity or non-identity of Metschnikoff's stimulines with the substances which form the subject of this communication, only mentioning here that the substances appear to me to be the same and that I have on this account adopted the name. The question as to whether they are correctly named, *i. e.* that they are substances which directly stimulate the cell to increased phagocytosis, is another point and, possibly, a still more debatable one.

The experiments were at first conducted by means of the method which I described in the 'British Medical Journal' of January 11th, 1902, but subsequently the modification of this method described by Wright and Douglas ('Proc. Royal Society,' vol. lxxii, p. 357, September 1st, 1903) was adopted in view of the opsonic power which these observers showed to be possessed by the blood fluids. I may shortly describe these two procedures in order to render the subjoined experiments more easy of comprehension. In the first series—my original technique—one vol. of the blood of the observer was drawn directly into a capillary pipette and at once mixed with an equal vol. of a suspension of an agar culture of the germs to be tested, prepared with normal saline solution; a fraction of a vol. of salt solution was further added to correspond to the vol. of immune serum added in the case of Tube No. 2. This first mixture of blood and germs was used as a control and a drop was at once placed on a slide, covered with a cover-glass, and placed in a moist chamber at 37° C. for fifteen minutes. A second film was then prepared in precisely the same manner, with the exception that a fraction of a vol. of immune serum was added to the mixture of blood and germ suspension. The two drops were usually placed on the same slide, side by side, and incubated together. At the end of fifteen minutes the cover-glasses were slid off the slide, and the blood-film left behind was dried and stained by my modification of Romanowsky's method. The average number of

bacteria ingested by the polynuclear leucocytes was ascertained and the results of the two films contrasted. In this way the effects of the addition of immune serum were readily detected and measured.

The subsequent discovery of opsonins by Wright and Douglas, however, made it possible that the increased phagocytosis which I had found might have been due to the presence of opsonins, and in my subsequent experiments the modified technique of Wright and Douglas was adopted, as by this method it was possible to get rid of the opsonins from the blood-fluids by heating and to employ the heated serum or plasma in place of the fresh unaltered plasma used in my original technique.

Malta fever stimulins.

Experiment 1, *September* 25*th*, 1902.—The effect of adding to normal human blood a trace of serum derived from a man recently convalescent from Malta fever.

(*a*) i.	W. B. L.'s blood . . . 2 vols. *M. melitensis* suspension . . 2 „ Normal salt . . . . 1 vol.	Phag. Index—*i.e.* average number of germs phagocyted by each polynuclear . .	17·6
ii.	W. B. L.'s blood . . . 2 vols. *M. M.* suspension . . . 2 „ Malta fever serum . . . 1 vol.	Phag. Index . . .	70·
(*b*) i.	F. G.'s blood . . . . 2 vols. *M. M.* suspension . . . 2 „ Normal salt . . . . 1 vol.	Phag. Index . . .	3·1
ii.	F. G.'s blood . . . . 2 vols. *M. M.* suspension . . . 2 „ Malta fever serum . . . 1 vol.	Phag. Index . . .	43·
(*c*) i.	S. R. D.'s blood . . . 2 vols. *M. M.* suspension . . . 2 „ Normal salt . . . . 1 vol.	Phag. Index . . .	·4
ii.	S. R. D.'s blood . . . 2 vols. *M. M.* suspension . . . 2 „ Malta fever serum . . . 1 vol.	Phag. Index . . .	4·5

Experiment 2, *July* 13*th*, 1903.—The effect of adding to normal human blood a trace of serum derived from a rabbit immunised to Malta fever.

i.	W. B. L.'s blood . . . 2 vols. *M. M.* suspension . . . 2 „ Normal salt . . . . ½ vol.	Phag. Index . . .	4·7

ii.	W. B. L.'s blood . . .	2 vols.	
	M.M. suspension . . .	2 „	Phag. Index . . . 15·2
	Immune rabbit's serum (diluted 1 in 10)	½ vol.	
iii.	W. B. L.'s blood . . .	2 vols.	
	M. M. suspension . . .	2 „	Phag. Index . . . ·5
	Normal rabbit's serum (diluted 1 in 10)	½ vol.	
iv.	W. B. L.'s blood . . .	2 vols.	
	M. M. suspension . . .	2 „	Phag. Index . . . 1·8
	Normal human serum (diluted 1 in 10)	½ vol.	

Experiment 3, *July* 14*th*, 1903.—The same serum as Experiment 2, with the exception that the sera employed in the former experiment had been allowed to stand for twenty-four hours and were then heated to 60° C. for ten minutes before being diluted and added to W. B. L.'s fresh blood.

i.	W. B. L.'s blood alone	Phag. Index 3
ii.	„ „ + heated immune rabbit's serum .	„ 15
iii.	„ „ + heated normal rabbit's serum .	„ 3·8
iv.	„ „ + heated human serum . .	„ 1·7

Experiments 1 and 2 show that the addition to normal human blood of a trace of Malta fever serum, whether derived from a man or an immunised animal, has a powerful effect in inducing increased phagocytosis of the *Micrococcus melitensis* by the normal human leucocytes. Experiment 3 further showed that this effect is in no way impaired if the immune serum be heated to 60° C. Control experiments, which it is unnecessary to record in detail, were performed substituting other germs for the *Micrococcus melitensis*, but in no case was there any evidence of a stimulin effect.

Typhoid stimulins.

Experiment 4, *September* 30*th*, 1902.—The effect of adding to normal human blood a trace of serum derived from a convalescent typhoid patient.

i.	W. B. L.'s blood . . .	2 vols.	
	B. typhosus suspension . .	2 „	Phag. Index . . . 8·2
	Normal salt solution . .	1 vol.	
ii.	W. B. L.'s blood . . .	2 vols.	
	B. typhosus suspension . .	2 „	Phag. Index . . 19·1
	Typhoid serum . . .	1 vol.	

iii. W. B. L.'s blood . . . 2 vols. *B. typhosus* suspension . . 2 „ Malta fever serum . . . 1 vol.	Phag. Index . .	1·5

Experiment 5, *July* 10*th*, 1903.—The effect of adding to normal human blood a trace of serum derived from a rabbit immunised with *B. typhosus*.

i. W. B. L.'s blood . . . 2 vols. *B. typhosus* suspension . . 2 „ Normal salt solution . . 1 vol.	Phag. Index . . .	5·4
ii. W. B. L.'s blood . . . 2 vols. *B. typhosus* suspension . . 2 „ Immune rabbit's serum (diluted 1 in 10) . . . . . 1 vol.	Phag. Index . . .	19·5
iii. W. B. L.'s blood . . . 2 vols. *B. typhosus* suspension . . 2 „ Normal human serum (diluted 1 in 10) . . . . . 1 vol.	Phag. Index . . .	3·1

Experiment 6, *July* 11*th*, 1903.—The same series as in Experiment 5, with the exception that the sera employed in the former experiment had been allowed to stand for twenty-four hours and were then heated to 60° C. for ten minutes before being diluted and added to W. B. L.'s fresh blood.

i.	W. B. L.'s blood alone	Phag. Index 2·3
ii.	„ „ + heated immune rabbit's serum .	„ 8
iii.	„ „ + heated normal human serum .	„ 2·3

Experiments 4 and 5, which are comparable with Experiments 1 and 2, conducted with Malta fever germs and sera, show, therefore, that a trace of immune typhoid serum, whether derived from a convalescent man or an immunised animal, when added to normal human blood is capable of stimulating the leucocytes of that blood to increased phagocytic activity against typhoid bacilli. Heating to 60° C., as in the case of Malta fever sera, does not appear to diminish the stimulating properties of such immune typhoid sera.

Experiment 7, *July* 15*th*, 1903.—Effects of adding a trace of typhoid serum derived from an immunised rabbit to the fresh blood of a normal rabbit, contrasted with the effects of adding normal rabbit's serum to the fresh blood of a typhoid rabbit.

(*a*)	i. Typhoid rabbit's blood . . 2 vols. *B. typhosus* suspension . . 2 „ Normal salt solution . . 1 vol.	Phag. Index . .	5·5

ii.	Typhoid rabbit's blood . .	2 vols.	
	B. typhosus suspension . .	2 „	Phag. Index . . . 5·2
	Normal rabbit's serum (diluted 1 in 10)	1 vol.	
(*b*) i.	Normal rabbit's blood . .	2 vols.	
	B. typhosus suspension . .	2 „	Phag. Index . . . 3·6
	Normal salt solution . .	1 vol.	
ii.	Normal rabbit's blood . .	2 vols.	
	B. typhosus suspension . .	2 „	Phag. Index . . . 9·
	Typhoid rabbit's serum (diluted 1 in 10)	1 vol.	

This experiment, in which it will be noted that the leucocytes of the rabbits were employed instead of, as in the other experiments, human leucocytes, shows once more the same effect of the addition of immune serum, the phagocytic activity of the normal rabbit's blood being increased nearly threefold, while in the control experiment the addition of normal serum to the immune rabbit's blood was without effect.

Wright and Douglas subsequently published an account of their experiments upon the nature of phagocytic action, in which they demonstrated that, in the case of most of the germs which they investigated, the phagocytic power of the leucocytes was dependent upon the manner in which the germs had been acted upon by certain substances contained in the blood-fluids to which they gave the name of *Opsonins*. These opsonins they further showed to be specific and to be destroyed by heating to a temperature of 60° C. for ten minutes. It was therefore possible that the results recorded above might have been in part or altogether due to the opsonic action of the blood-fluids employed in the experiments. The modification of my original technique which was used by Wright and Douglas was accordingly adopted in the following experiments for the purpose of determining whether opsonic action played any part in the mechanism of these stimulin effects. In place of the whole blood the normal human corpuscles, red and white, were freed from the plasma by citration and repeated washing in normal saline solution. To these washed corpuscles the various sera which were separately collected were subsequently added together with the suspension of germs, and the mixtures were incubated in capillary tubes instead of between a cover-glass and a slide. Films were subsequently made on slides, the rest of the technique being the same as before. In

this way it was possible to heat a serum to 60° C. before adding it to the washed corpuscles and thus to destroy any opsonins contained in it. In the following experiments, therefore, all the sera employed, both in the stimulin experiments and the controls, were heated to 60° C. for ten minutes, and therefore contained no active, thermolabile opsonins. It is possible that traces of active opsonin may have adhered to the corpuscles, but owing to the repeated washings and centrifugalisations to which they had been subjected, this appears unlikely.

Experiment 8.—Effects of adding a trace of heated immune serum, derived from immunised typhoid rabbit, to the washed corpuscles and heated serum of a normal man.

i. F. G.'s corpuscles . . . 3 vols. „ heated serum . . 3 „ *B. typhosus* suspension . . 1 vol.	Phag. Index . . .	3·2
ii. F. G.'s corpuscles . . . 3 vols. „ heated serum . . 2 „ Typhoid rabbit's heated serum (diluted 1 in 5) . . . 1 vol. *B. typhosus* suspension . . 1 „	Phag. Index . . .	11·

The above experiment, which demonstrates the same stimulin effect as that recorded in Experiment 5, conducted with the original technique, like the majority of the other experiments detailed, has been repeated many times and the results are always the same, the stimulin effect being seldom less than that recorded above and frequently greater.

Experiment 9.—Effects of adding a trace of heated typhoid serum derived from a severe case of typhoid fever to the washed corpuscles and heated serum of a normal man.

(*a*)	i. F. G.'s corpuscles . . . 3 vols. „ heated serum . . 3 „ *B. typhosus* suspension . . 1 vol.	Phag. Index . . .	2·8
	ii. F. G.'s corpuscles . . . 3 vols. „ heated serum . . 2 „ Typhoid patient's heated serum (diluted 1 in 5) . . . 1 vol. *B. typhosus* suspension . . 1 „	Phag. Index . . .	17·4
(*b*)	i. J. M. W.'s corpuscles . . 3 vols. „ heated serum . . 3 „ *B. typhosus* suspension . . 1 vol.	Phag. Index . . .	6·4
	ii. J. M. W.'s corpuscles . . 3 vols. „ heated serum . . 2 „ Typhoid patient's heated serum (diluted 1 in 5) . . . 1 vol. *B. typhosus* suspension . . 1 „	Phag. Index . . .	22·7

This experiment, like No. 8, shows that a typhoid immune serum when freed from its thermolabile opsonin is still capable of stimulating phagocytosis when a trace is added to the heated serum and washed corpuscles of a normal individual.

With regard to the nature of the stimulin effect demonstrated by the above experiments, the possibility of its being due to agglutination must be considered. The immune sera employed all contained specific agglutinins, some of them in considerable amount, and, theoretically, the increased phagocytosis might be merely the result of the formation of small clumps of bacilli which were ingested by the polynuclears as readily as single germs and in this manner increased the phagocytic index. That this may account in some small degree for the phenomena is, I think, probable, but it does not appear a sufficient explanation, for the following reasons. In the first place, the degree of stimulation bears no relation to the quantity of agglutinins present in the immune serum, a highly agglutinating serum occasionally giving a negative or a very slight stimulin effect, while one poor in agglutinins may treble or quadruple the normal phagocytic power. Again, the effects of agglutination, if marked, should be in evidence in the stained films; but this was only rarely noted, the bacilli in the majority of cases being isolated and more or less evenly distributed throughout the film. The high dilution of the immune serum in the mixtures, and the short period of contact appear sufficient to account for this absence of visible agglutination in the stained films.

An attempt was made by a further experiment to determine whether the increased phagocytosis was due to a true stimulation of the leucocytes or to these substances acting directly upon the bacteria and rendering them more susceptible to the phagocytic power of the leucocytes—in other words, whether they acted in the same manner as the thermolabile opsonins of Wright and Douglas. In this experiment the whole of the sera employed had been previously heated to 60° C., and therefore contained no thermolabile opsonin. A suspension of typhoid bacilli was first divided into three equal portions—"A," "B," and "C." "A" suspension was untreated. "B" suspension was mixed with 0·5 c.c. of heated typhoid serum, derived from an immunised rabbit, and the mixture was allowed to digest for one hour at 37° C. At the end of this time it was centrifuged until the supernatant fluid

was glass-clear; this was pipetted off and replaced by normal saline, in which the germs were once more shaken up and the centrifuge again employed. After the washing to remove the remains of the serum, the supernatant salt solution was removed and a fresh quantity added to bring the suspension up to its original volume. In this way the germs had been given the opportunity of absorbing or "fixing" the substance contained in the heated immune serum, if they were capable of doing so. The third portion—suspension "C"—was treated in a manner precisely similar to "B," with the exception that heated serum from a normal rabbit was employed in place of the typhoid rabbit's serum. Three experiments were then done with each of these three suspensions, normal human leucocytes and normal heated human serum being employed in each case.

Experiment 10.

		Suspension "A" (untreated).	"B" (digested with typhoid serum).	"C" (digested with normal serum).
(*a*)	F. G.'s corpuscles . . 3 vols. „ heated serum . 3 „	Phag. Index, 38	23	35
(*b*)	F. G.'s corpuscles . . 3 vols. „ heated serum . 2 „ Typhoid rabbit's heated serum (diluted 1 in 2) 1 vol.	„ 76	49	70
(*c*)	F. G.'s corpuscles . . 3 vols. „ heated serum . 2 „ Normal rabbit's heated serum (diluted 1 in 2) 1 vol.	„ 43	28	34

The high readings of these experiments were due to the suspensions being rather too thick, but this did not influence the results further than increasing the labour of counting the films. It will be seen that here the same experiment is repeated three times, with, in each instance, a different suspension of typhoid germs—"A," "B," and "C." With the untreated suspension "A" a twofold increase of phagocytosis results from the addition of the typhoid serum, while a precisely similar effect is obtained with suspensions "B" and "C," which had been treated with typhoid serum and normal serum respectively. Had the substance contained in the typhoid serum been fixed by the bacteria of suspension "B" and had the mechanism of phagocytosis been similar to what Wright and Douglas have shown to be the case in opsonic action, I should have expected the experi-

ment conducted with this emulsion to have shown throughout higher phagocytic indices than in the case of those performed with suspensions "A" and "C," and, further, that the degree of stimulin effect, as compared with the two controls, would have been less. In place of this, phagocytosis with "B" suspension is less than with the others, while the stimulin effect of the addition of typhoid serum is precisely the same. Without wishing to insist too strongly upon the results of this experiment, it appears to me to suggest that the effects recorded above are due to a real stimulation of the leucocytes by the immune serum and are not the results of a sensitising action of the serum upon the bacteria similar to the action of opsonins.

The conclusions to which the above experiments, and many others of a similar nature, have led me, may be shortly summarised as follows:

(1) Sera derived from cases of Malta fever or enteric fever, or from animals immunised with living cultures of the germs of these diseases, contain substances which, when added to normal human blood, are capable of increasing the phagocytic activity of the leucocytes of that blood.

(2) These substances are specific; *i. e.* they will only induce increased phagocytosis of the germ which has been used in immunisation.

(3) The substances are thermostable, withstanding a temperature of 60° C. maintained for fifteen minutes.

(4) No evidence of the presence of these substances could be found in the sera of normal men or animals.

(5) Although the increased phagocytosis may in some part be due to the presence in the sera of agglutinins or of immune body, the substances in question do not appear to be identical with these.

(6) Experiment No. 10 would appear to suggest that these substances act directly upon the leucocytes, and not upon the bacilli.

With regard to the identity of these substances with the "stimulines" of Metschnikoff, it is difficult to be sure. His experiments and those of Gengou, Klemperer, Besredka, and others were conducted on the living animal, and without any system of quantitative measurement; it is not easy therefore to contrast them with those recorded above. The substances are, however, identical so far as their thermostability is concerned, and the chief point of apparent difference is that I have been unable to

obtain any evidence of an increased phagocytosis as the result of the addition of a normal serum to the normal blood of another species, while in the case of Metschnikoff's stimulines such an effect was frequently observed.

Postscript.—Since my description of these experiments at the Pathological Society, Dr. A. E. Wright has been good enough to communicate to me the gist of a discussion which he has recently had upon this subject with M. Metschnikoff. From this I learn that M. Metschnikoff is inclined to abandon the use of the term "stimulines" for the thermostable substances which promote phagocytosis and to adopt in preference the term "sensitisers" or "opsonic sensitisers." In the discussion which followed my remarks, Dr. Wright suggested that the substances whose action was demonstrated by my experiments might possibly be thermostable opsonins—that is, similar in their mode of action to opsonins but differing from them in being thermostable. It is quite possible that such may prove to be their nature, and I am far from suggesting that the above experiments can be considered as settling the question as to whether these substances act upon the leucocytes or upon the bacteria.

My reasons for employing the word "stimulin" in referring to these substances depended more upon my conviction of their identity with Metschnikoff's "stimulines" than upon any certainty as to their stimulating action on the leucocytes, but I think it is obvious that further experimental proof is needed as to the manner in which these substances produce their effects before they can be accurately labelled with a descriptive name.

March 21st, 1905.

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37. *Myasthenia gravis.*

By E. Farquhar Buzzard.

[With Plate II.]

De quibusdam læsionibus in Myastheniâ gravi *repertis.*
Cum Tabulâ II.

Summarium.

Quinque casibus indagatis, in omnibus inventi sunt lymphocyti in musculis striatis inter fibras collecti.

Hae lymphocytorum collectiones facilius in musculis ocularibus demonstrari possunt.

In glandulâ thyreoideâ, in jecore, et in glandulis adrenalibus quoque adsunt.

Musculorum fibræ aliquatenus degeneratæ sunt.

In glandulâ thymo, a L. S. Dudgeon examinatâ, nulla læsio notabilis reperta est.

Hæc sententiam a nonnullis propositam haud confirmant, sententiam quod casus quidam *Myastheniæ gravis* ex lympho-sarcomate glandulæ thymi constant cum neoplasmatibus secundariis in musculis conjuncto.

Cur colligantur lymphocyti explicare difficile est, quum ægrotantium sanguis nihil abnorme microscopice monstraret.

Lymphocytorum collectiones, deinde, per se vix causare possunt aut paralysem aut fatigationem hujus morbi proprias.

Myasthenia gravis can no longer be considered a pathological curiosity nor, indeed, a very rare disease, and owing to the variety and often localised nature of its symptoms its recognition from a clinical standpoint is of importance to those who practise in many different branches of medicine and surgery. That in itself would be sufficient reason for bringing the subject of its morbid anatomy before this Society, but I venture to think that the results of my work upon it provide material of interest not only to the neurologist but to the general pathologist.

Let me remind you that Myasthenia gravis is a very fatal disease which may run an acute, a sub-acute, or a chronic course, its duration varying roughly between a few weeks and ten or more years. One might almost say that it has only one clinical feature, the diminution or abolition of the capacity on the part of a smaller or larger number of voluntary muscles to prolonged contraction under the influence of the will or of faradism, associated with the normal sharp response of the same muscles to single short stimuli such as are produced by the make and break of a gal-

vanic current. Further reference to the clinical side of the disease would be out of place here, and I will proceed at once to give in a very brief form the facts which have been known up to the present time concerning its morbid anatomy.

Naturally the central and peripheral nervous system has been thoroughly investigated by a number of competent observers, but always with scanty results. A few have found chromatolysis of nerve-cells and a few others slight degenerative alterations, but the large majority have been unable to find changes of such a nature as would account for the symptoms of a subacute or chronic disease either in the central or peripheral parts of the nervous system. Some authors have expressed themselves strongly in favour of the view that the lesion must be situated in the neuro-muscular connections, but no histological support of this theory has been produced. Within the last few years Weigert, Goldflam, Hun, Link, and others have found important morbid changes outside the nervous system. These consist in tumours of the thymus gland, resembling lymphosarcomata, or merely persistent enlarged thymus glands associated, in some cases, with infiltration of muscles by lymphoid tissue. Since these findings have been recorded similar changes have been reported in an increasing number of cases, and they are particularly interesting when taken into comparison with my own results.

During the last two or three years I have had the opportunity of examining *post-mortem* five cases of Myasthenia gravis, and for permission to make use of them I am indebted to Dr. T. Buzzard, Dr. Ormerod, Dr. Henry Head, and Dr. Cecil Wall. My thanks are especially due to Dr. Head and Dr. Wall, who kindly placed the *post-mortem* examination of two cases under their care at the London Hospital in my hands.

Of these 5 cases 3 were men and 2 were women. The eldest was 45 and the youngest 29 years of age at the time of death. The duration of illness was in one case twelve years, in another two years, in another eighteen months, in another one year, and in the most recent only three months.

In no one of these cases was there noticed any congenital abnormality such as has been described occasionally and has led Oppenheim to regard the disease as congenital in origin. The naked-eye examination of the bodies revealed nothing of

any importance in 3 out of the 5 cases; in the other 2 the condition of the thymus gland alone called for some remark.

Mrs. S—, aged 29 years, died of respiratory failure after eighteen months' illness. During life the presence of some tumour in the anterior mediastinum had been suspected on account of the diminished resonance to percussion over the manubrium sterni. *Post mortem* a large thymus gland was found in the usual situation weighing 41 grammes and presenting the characteristic bilobar appearance which is seen in the young animal.

Mr. L. S. Dudgeon, who has kindly examined my sections of the thymus tissue in several of these cases, has reported on the histological character of this gland in the following terms:

"The cortex and medulla are clearly differentiated. Under a low power the gland presents a natural appearance, and there is no evidence of fibrosis. The cellular constituents show a normal structure, but in this connection there is one point of great interest. Although the gland is enlarged and of healthy appearance, there is a complete absence of eosinophile cells such as we meet with in the large thymus glands of children and young animals. These cells, so often present in very large numbers along the septa and around the blood-vessels, are entirely wanting. The only condition in which I have found them to be few in number or even absent, if the thymus is enlarged, is in cases of hypertrophy of the adult gland. Many of the Hassall's corpuscles are degenerated and some contain large calcareous masses. Hyaline degeneration is also extremely well marked in some, and others have quite a clear centre surrounded by only a few cells at the periphery. Numerous hæmorrhages occur in the gland tissue, and the small blood-vessels are very congested in certain parts. This resembles what is found in the thymus glands of children who have died of pneumonia or empyema or some disease associated with an increase of intrathoracic pressure."

The other case in which the thymus presented abnormal features was that of a man, aged 40 years, who died after three months' illness in the London Hospital, where he was under the care of Dr. Wall. Here the condition was quite different. A large mass, weighing 59 gr., lay in the anterior mediastinum and occupied the position of the thymus gland. Its shape

roughly resembled that of the thymus, although it was not distinctly lobulated. The upper part of the mass had all the appearances of a new growth and was firmly adherent to the vessels behind it. Portions of it were moderately firm, but others on section presented a semi-fluid consistence not unlike very thick pus. Films of this material showed that it consisted of cells, the great majority of which had the appearance of small lymphocytes. The lower part of the mass was not so adherent to surrounding structures and on section was seen to be a multilocular cyst filled with a cloudy fluid which also contained quantities of small mononuclear cells with little protoplasm.

Histologically the *solid* part of this gland was composed of large masses of lymphoid tissue surrounded by strands of connective tissue, but the arrangement of the masses was not that of the lobulated normal gland, and there was an extreme paucity of concentric corpuscles. Sections of the *cystic* portion suggested a thymus gland from which the lymphoid cells had largely disappeared and been replaced by a thin fluid. The walls of the cysts resembled the trabeculæ of the gland but looked as if they had been compressed and had developed a false fibrous lining membrane. Numerous collections of round cells were present in the cyst walls themselves and a few concentric bodies. This mediastinal tumour was not associated with any noticeable enlargement of neighbouring glands nor with any infiltration of the lungs or other thoracic organs.

It will be convenient to refer here to the condition of the thymus tissue in the other patients. In the oldest case, aged 45 years, a man who had had the disease for twelve years, the gland was larger than usual and weighed 9 grams. According to Mr. Dudgeon, the cellular constituents were in good condition, and the cortex and medulla could be differentiated from each other. There was some increase in fibrous tissue, an absence of eosinophile cells and some replacement of glandular tissue by fat. Many of the concentric corpuscles were large and calcified, while others gave evidence of granular degeneration. In the two remaining cases only small islets of thymus glandular remains could be seen scattered throughout dense connective and adipose tissue. The cortex could not be distinguished from the medulla, and concentric corpuscles were either healthy or had undergone granular or calcareous changes. In

other words, these remnants of gland tissue were identical with what is found in normal adult life.

Owing to the absence of macroscopical changes to guide one the microscopical examination of these cases has been a very laborious task. Some thousands of sections taken from the central and peripheral nervous system, from the muscles, and from all the important glandular and other organs in the body, have been prepared and examined. The accompanying illustrations represent the characteristic changes found to a greater or less extent in all the cases.

The examination of the brain, cord, and peripheral nerves showed no evidence of fibre degeneration either by the Marchi or by the Weigert-Pal stains. Sections from the motor cortex, the cranial nerve nuclei, the spinal grey matter, and the posterior root ganglia, studied by the Nissl method, showed no constant changes of importance, although it can hardly be said that all were perfectly healthy.

In one case there were a few recent capillary hæmorrhages in the floor of the fourth ventricle, and in all cases the vessels of the brain and cord were somewhat congested, but these findings cannot be considered unnatural when it is remembered that death was invariably associated with a condition of asphyxiation due to failure of the respiratory musculature.

In the first dorsal posterior root ganglion of one case was found a small focus of lymphocytes scattered among the ganglion cells. This collection of cells resembled those which were found in certain muscles, and which have proved to be of common occurrence in many parts of the body in all these five cases.

Wherever they were found these foci of lymphocytes were essentially similar in their characteristics, and I propose for the sake of brevity and convenience to call them "lymphorrhages." This name is selected for two reasons: (1) because the cells of which they are almost exclusively composed are indistinguishable from small lymphocytes; that is to say, they are of the size of the small lymphocytes of the blood, they are generally round or slightly oval, and they contain a relatively large round single nucleus surrounded by a minimal amount of protoplasm; (2) because their appearance reminds one of capillary hæmorrhages, with the distinction that the cells are of the kind described and

not red blood corpuscles. I use the term "capillary hæmorrhage" advisedly on account of the fact that it is not unusual to find in the immediate neighbourhood of these cells an empty capillary vessel the wall of which is composed of a single layer of endothelial cells. The whole picture suggests that a small capillary has been overloaded at a certain point with lymphocytes and that it has burst, scattering its contents quite irregularly into the surrounding tissues. I am not satisfied whether the capillary vessels found in association with these lymphorrhages are lymphatic or vascular, but I am inclined to regard them as blood-capillaries for the reason that a few polymorphonuclear leucocytes and sometimes a few red corpuscles are occasionally found scattered among the lymphocytes.

A very large number of sections of voluntary muscles stained by hæmatoxylin and eosin or by van Gieson's method were examined, and I was able to assure myself that lymphorrhages were present in some muscles in all five of my cases. The ease with which they were found varied very considerably; it may be because they were more numerous in one case than another, or perhaps because the muscles which were removed for examination were more or less suitable. For instance, there was no difficulty in finding these lymphocytic deposits in the ocular muscles of the three cases from which I took those muscles. Their small size made it possible to examine them thoroughly. In the longest standing case only very few lymphorrhages were found in the muscles investigated, but the autopsy was performed under difficult circumstances, and portions of only a few of the larger limb muscles were obtained. In the illustrations it will be noticed that the cells are scattered between the muscle-fibres, and that they do not, as a rule, actually invade the latter. In the majority of instances the muscle-fibres in the immediate neighbourhood are of healthy appearance, retaining their striation and normal calibre. In one section, however, there was present the remains of a large lymphorrhage, and in addition very marked changes in the contiguous fibres. These changes I have also observed frequently in other sections, apart from the immediate presence of lymphorrhages; the fibres are seen in cross-section to be swollen and rounded, irregular in size, and often less homogeneous than is normally the case. Some of them have a faintly granular or hyaline

appearance, and these may exhibit a tendency to take a paler and more yellow hue with eosin or fuchsin stains than do their healthy neighbours. Such changes may be seen in single fibres or in a small bundle of fibres, but I have never seen them general throughout any particular section. More severe alterations in the form of atrophy and nuclear proliferation have not been observed.

The examination of non-striated muscle has given negative results, but cardiac muscle has in more than one case been found to contain lymphorrhages without definite alteration of the fibres.

Leaving the nervous and muscular structures, the findings in various other organs must now be mentioned.

The *thyroid* gland was examined in three cases. In two of these there were definite lymphorrhages. Dr. Chalmers Watson, to whom I submitted one of the glands, has kindly sent me the following report: "The gland shows (*a*) distinct interstitial fibrosis; (*b*) numerous areas of cellular infiltration, which resemble small abscesses; (*c*) a large area of colloid degeneration of the fibrous stroma of the gland; (*d*) proliferation of the epithelium in parts, with formation of new vesicles; and (*e*) enlargement of spaces in parts, as in simple goitre."

The *liver* was examined microscopically in four cases, and in three of these it was healthy, except for the presence of lymphorrhages. The latter were numerous in some sections, and were found sometimes in the middle of lobules away from the bile-tracts and sometimes in the connective tissue of Glisson's capsule. The larger ones occurring in the midst of the hepatic cells caused a considerable amount of destruction or fatty degeneration of the latter. Small collections of lymphocytes in other parts were observed to lie among healthy liver-cells. In one case portions of Glisson's capsule showed wide spaces filled with *débris*, in the midst of which were numbers of lymphocytes along with other cells containing irregularly-shaped nuclei. Possibly these represented lymphorrhages of older date, in which the cells were undergoing changes.

The *spleen* was examined in each case, but did not present any unusual features; the organ was usually of firm consistence and the Malpighian bodies well marked.

The *kidneys* were also examined, but, apart from a somewhat

EXPLANATION OF PLATE II,

Illustrating the communication by Dr. E. F. Buzzard on "Myasthenia Gravis." (P. 355.)

Fig. 1.—A section of the adrenal body from a case of Myasthenia gravis, showing a collection of lymphocytes between the gland-cells.

Fig. 2.—A transverse section of one of the ocular muscles from a case of Myasthenia gravis showing collections of lymphocytes between the muscle-fibres and nerves.

TABULA II,

Ad dissertationem "De Myasthenià grave" illustrandam.

E. F. Buzzard. (P. 355.)

Figura 1.—Sectio microscopica corporis adrenalis. Monstrantur lymphocytorum collectiones inter glandulæ cellulas.

Figura 2.—Sectio microscopica unius e musculis ocularibus. Inter musculi fibras colliguntur lymphocyti.

Fig. 1

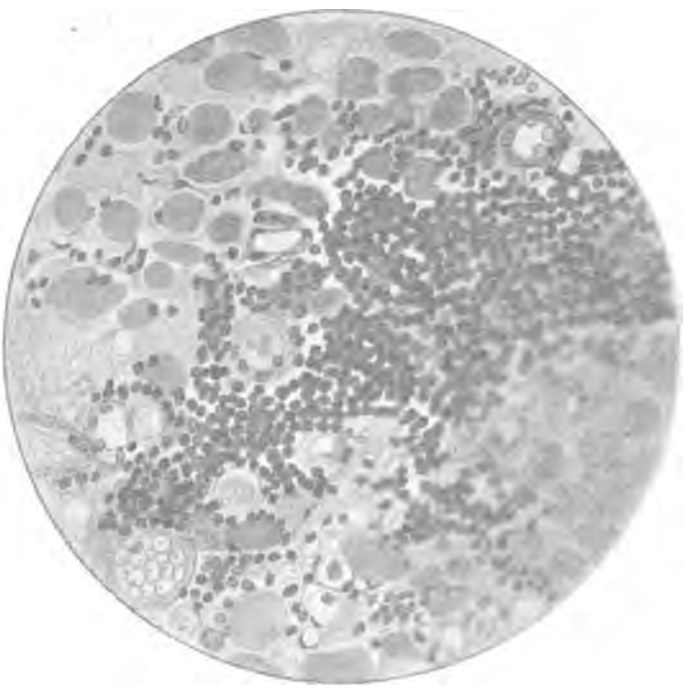

Fig. 2.

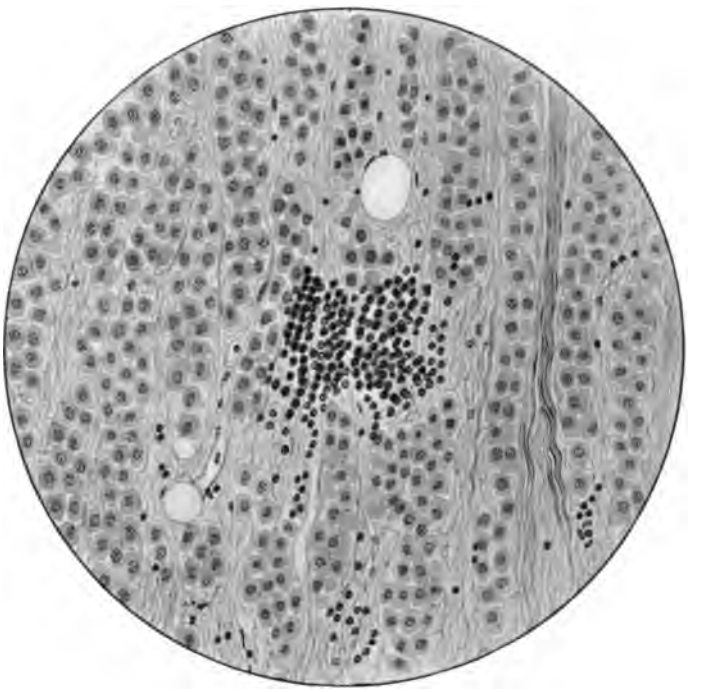

Fig. 1.

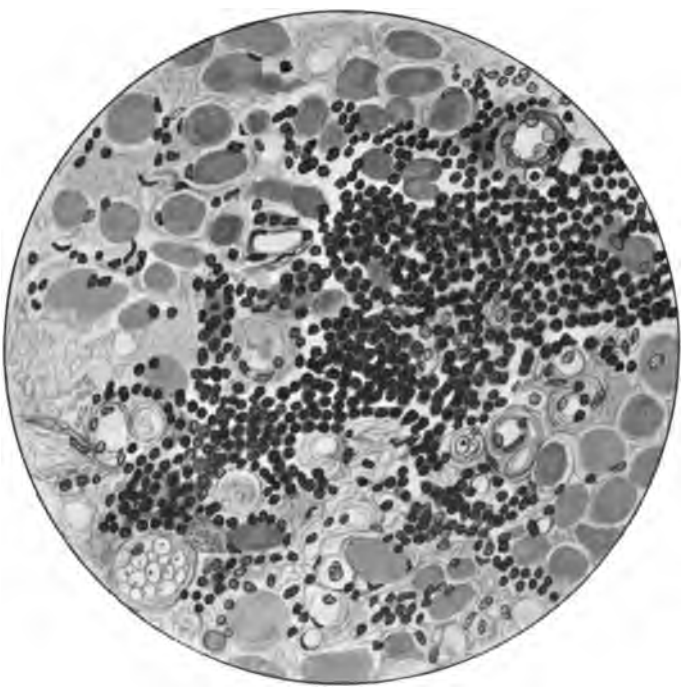

Fig. 2.

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doubtful excess of cells between the convoluted tubules in certain places, appeared to be healthy.

The *adrenal bodies* were carefully investigated in all five cases and each one showed the presence of more or less numerous lymphorrhages. They occurred indiscriminately in all parts of the medulla and cortex, and in the majority of instances did not seem to produce any reaction in the neighbouring gland-cells. In other respects the adrenal bodies were healthy.

In one case the *pancreas* was much altered by *post-mortem* digestion, but in the others it did not differ from the normal and no lymphorrhages were observed in its substance. In the connective tissue surrounding one gland there were patches of small round-cell infiltration, resembling that of the thymus remains, but containing no Hassall's bodies.

Several *pituitary bodies* and one *pineal gland* were cut and stained, but without result.

There was no evidence of lymphatic glandular enlargement in any of the patients, and one or two small bronchial glands which were examined showed no histological abnormality.

The *blood* was examined during life in two or three of the cases, but the results agreed with what has been found by numerous other observers in the entire absence of any alterations in the number or character of the cells.

I regret that I am unable to furnish any information with regard to the *bone-marrow*, as I have only attempted to examine it in one case, and that attempt has, so far, not proved a great success. The marrow from the shaft of the femur in the most acute case showed no cellular structure and consisted entirely of fat.

The bare results of this investigation can be briefly summarised in the following way :

(*a*) In five consecutive cases of Myasthenia gravis there were constant morbid changes in the shape of lymphocytic deposits in skeletal muscles and glandular organs.

(*b*) In all five cases slight changes in muscle-fibres have occasionally been found—sometimes in direct association with the lymphocytic deposits and sometimes apart from the latter.

(*c*) No constant abnormality of the thymus gland was observed. In two cases the thymus remains were not different from what is normally found in adults ; in one case these

remains were more considerable than is usual at 45 years of age; in one case there was a remarkable hypertrophy of the gland, and in the last and most acute instance of the disease the thymus showed changes which were partly proliferative and partly degenerative in type.

From the above facts we may make certain deductions. In the first place, there are strong grounds for believing that this disease, contrary to what has hitherto been supposed, possesses a definite morbid anatomy. In saying this I am aware, of course, that many observers have failed to describe what has been found in the muscles and other organs of these five cases, but I am supported by the knowledge that I have had to examine a very large amount of material in order to establish their existence, and also by the belief that in pathological anatomy nothing is proved to be non-existent unless it has been particularly and thoroughly looked for without success.

In the second place, it is evident that these lymphocytic deposits which have previously been described in association with thymus tumours and enlargements are not necessarily associated with them and cannot, therefore, be regarded as originating from, or as metastatic products of, that gland when diseased.

It would seem, rather, that the thymus shares with other organs a liability to become the seat of lymphoid change, sometimes to an excessive degree, in the disease under consideration. This disposes of the contention that certain cases of myasthenia are really instances of lymphosarcoma of the thymus gland with metastases in the muscles, a view which, to my mind, is strongly contra-indicated by the invariably small size of these collections of lymphocytes in different cases of varying duration.

In the third place, the absence of blood-changes, or of any alteration in the more important parts of the lymphatic system, renders the origin of these lymphorrhages exceedingly obscure, so obscure, indeed, that I shall not make any attempt to explain it. Finally, the relation of the morbid anatomy to the clinical features of the disease is an interesting but very difficult subject. For reasons which it would take too long to discuss here, I am not favourably impressed with the view that these muscle deposits, by offering obstruction to the lymph circulation, are directly responsible for the paralysis or fatigue exhibited by

these patients. I would rather regard these cell-collections as an outward and visible sign of some more subtle—metabolic or chemical—influence and the actual muscular changes which I have observed as representing the extreme result of that influence on a few of the fibres offering the least resistance. In this connection we may perhaps hope for some light to be thrown on the anomalous muscular phenomena observed in Myasthenia gravis, by further developments of the recent work of Botazzi, Jotezko, and others, with regard to the functional duality of muscle and the differentiated influence of certain poisons on its fibrillar and protoplasmic constituents. *May 16th*, 1905.

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38. *On the occurrence of squamous epithelium in carcinoma of the body of the uterus.*

By R. D. KEITH.

THE subject of the occurrence of squamous epithelium in carcinomata of the body of the uterus is one which has received a certain amount of attention in late years, especially in Germany, and the following case may serve to throw some new light on the subject.

Shortly, the clinical history of the case is as follows:

The patient, a woman, aged 53 years, was admitted to the Frauenklinik, in Tübingen, in the end of December, 1904, complaining of symptoms which pointed to cancer of the body of the uterus, and which were first noticed by the patient about six months previously. The patient had been married for thirteen years, but had had no children, and there was no history of abortion. There was nothing else of note in her history. With regard to the physical signs the patient was in a fair state of nourishment; the tubes, broad ligaments, ovaries, and rectum were normal. The heart was markedly arythmic. On examination *per vaginam* there was a moderate escape of blood. The portio-vaginalis and external os were normal. The uterine body was of the size of a man's fist and was anteflexed and movable. In the left half of the body a roundish prominence could be felt.

Curetting of the uterine cavity for diagnostic purposes was

performed. In the course of this one felt that the uterine cavity was much roomier than normal, and with the curette a large amount of friable material was removed with ease. This material consisted of blood and of ragged pieces of tissue, which in size varied from that of a pea to that of a medium-sized bean. Three of the pieces presented to the naked eye the appearance of ordinary mucoid polypi. Microscopically, however, one found that all the fragments were composed of a stroma consisting of the remains of uterine muscle containing islands of pale squamous cells of various shapes and sizes, and with their nuclei often showing signs of chromatic degeneration. Traces of the glandular epithelium with the cylindrical cells arranged several layers deep were also present. No trace of the surface epithelium could be seen. The diagnosis of cancer of the body was made and the uterus was removed *per vaginam* by Professor Döderlein.

The vaginal route was in this case chosen in preference to the abdominal on account of the marked cardiac weakness making as short a period of anæsthesia as possible desirable. The operation presented considerable difficulty, partly on account of the narrowness and inelasticity of the atrophic nulliparous genital canal and partly on account of the size and hardness of the uterus; but by the aid of a paravaginal incision and longitudinal division of the uterus in the median line, it was rendered easier, and a good view of the field of operation was obtained. It was regrettable that owing to the vaginal method having to be adopted, no search for diseased glands could be made in this case.

Although the uterus was divided into two halves in the course of the operation, yet sufficiently accurate measurements and observations could be made. From os externum to fundus the uterine cavity measured 7 cm., and from internal os to fundus 5 cm. With the exception of a narrow smooth strip extending from the uterine opening of the right Fallopian tube to the os internum the surface of the uterine cavity was clothed with ragged villous masses of friable tissue. The chief tumour mass was situated in the posterior wall, but the malignant process had extended over the fundus and had involved the upper half of the anterior wall on its internal surface. The chief tumour mass was round in shape and extended from the fundus to within 1 cm. from the os internum, involving the posterior wall and reaching at one point almost to the peritoneal surface, its dia-

meter being 4 cm. It was to the naked eye clearly demarcated from the uterine tissue, and its cut surface had a glistening white appearance and gave somewhat the impression of a honeycomb, the remains of the uterine muscle enclosing the polygonal spaces filled with friable material which could be squeezed out with ease. The uterine wall at the right superior cornu was intact and measured here 1·5 cm.

The cervical canal, the portio vaginalis, and the ovaries were entirely normal.

Microscopically the tumour was composed of three chief types of cells, one type columnar glandular, the second squamous, while the third consisted of cells which must be regarded as intermediate between the other two.

The first class of cells formed a characteristic malignant adenoma. The uterine glands had undergone an extreme degree of proliferation; the separate glandular cavities could not be distinguished one from another, being connected with each other by a series of communicating spaces, and their high cylindrical cells which were in many places arranged in several layers, lay *dos-à-dos* and showed here and there irregularities in their shape as well as nuclear changes. In some places this malignant adenomatous condition was confined to a narrow layer on the surface of the tumour, in fact, in sections from one part no appearance of it could be seen, while in other places it had penetrated far into the uterine wall, destroying its substance. Apart from those which showed degeneration the nuclei of these cells were elongated and deeply stained with hæmatoxylin and the cell bodies also to some extent took that stain. It is possible that in those places where no appearance of malignant adenoma was to be seen it had been removed in the course of curetting.

The greater part of the tumour, however, was composed of the second type of cells, and the masses formed by these were situated as a rule deeper in the uterine tissue—that is, nearer the peritoneal surface—than the glandular part of the tumour, but here and there cells of this type were found either singly or in small groups among the cylindrical cells.

With regard to these cells, at first sight they appeared to be undoubtedly of a squamous epithelial type. In shape they were mostly polyhedral and their boundaries well demarcated, but

in some parts they assumed an elongated shape and in others no cell boundaries were to be seen. They varied much in size. The cell protoplasm stained lightly with eosin, while the nuclei varied greatly in their reaction towards hæmatoxylin. Some were very large and vesicular and stained only very lightly, while others were exceedingly small, appearing like a small black speck in the centre of the pale cell protoplasm. Such stained very deeply and over all chromatic changes were numerous. The cell inclusions described by Leopold (1) and Rosenthal (2) could also be seen. No true cancer pearls were present, but structures closely resembling these were to be seen.

The third type of cells were oval or round in shape and were intermediate in size between the tall columnar cells and those of the squamous type. Their granular nuclei were relatively to the cell bodies of large size, and though not staining so deeply as those of the cylindrical cells, yet on the whole were much more intensely stained than those of the squamous type. Chromatic changes were not nearly so numerous as in those cells of the latter class. In some places these cells were arranged in irregular masses, while in other parts they lay in long columns several abreast, these columns being separated by a few strands of the remaining muscular tissue. They probably indicated the advance of the cancer along dilated lymph spaces and had penetrated through the uterine muscle to close under the peritoneal coat. Here and there among these were found cells belonging to the squamous type, and in other places occurred structures of an alveolar nature probably representing the malignant adenoma. In places this third type of cells seemed on the one hand to be formed by a gradual change in shape from those of the malignant adenoma, while on the other hand they seemed in parts to fade off gradually into the squamous type. This, however, was not the case throughout, as here and there the cylindrical and squamous cells adjoined one another by an extremely sharp border without the interpolation of an intermediate type.

Throughout the tumour marked signs of calcareous degeneration were present, and in some sections the large number of empty spaces seemed to indicate that the calcareous masses had fallen out or had been dissolved by the acid alcohol. A marked small round-cell infiltration was present throughout the tumour.

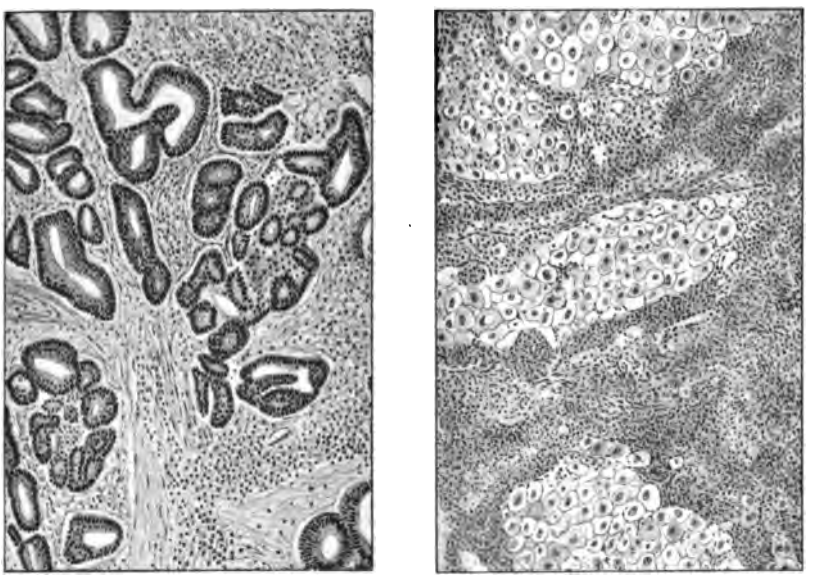
Cases of a similar nature, in which apparently a squamous

epithelioma occurred in the body of the uterus along with one of a glandular nature have been described by Eckhardt (3), Kaufmann (4), Hofmeier (5), Lehmann (6), Fränkel and Wiener (7), and Hitschmann (8). Lewers (9) has also described a case of keratinising cancer of the body of the uterus.

With regard to the origin of such a condition four possibilities might be put forward:

(1) The two separate forms of tumour-cells may arise from

FIG. 60.



The figure shows on the right-hand side the squamous-celled portion of the growth, and on the left the columnar-celled.

two different forms of epithelium, the two tumours so formed developing together and becoming in places intimately mixed. Winter (10) considers that this can take place, and cites as examples the cases of Kaufmann and Hofmeier. With regard to squamous cancers of the body of the uterus in general Winter (11) regards them as arising from a primary "epidermoidalisierung" of the mucous membrane—that is, the conversion of the columnar epithelium of the uterine mucous membrane into squamous. Gebhard (12), however, considered that this process, which Ruge and Veit (13) describe as occurring in cases of

cancer of the cervix, is merely a superficial extension of the cancerous process over the surface of the uterine cavity. In our case the cervix and portio were absolutely normal. In the body of the uterus, however, the replacing of the columnar epithelium by that of a squamous type has been described apart from the condition known as "epidermoidalisierung," *e. g.* Mainzer (14) observed such a condition in four cases which had been treated with either atmokausis or strong formalin, and two of these showed appearances markedly suspicious of cancer. v. Friedländer (15) observed in the uterus of a child which had died from nephritis complicating scarlet fever, epithelium of a squamous type replacing the original uterine epithelium over a considerable area. v. Rosthorn (16) extirpated a uterus the epithelium of which was of a squamous nature and which in places showed appearances indicating a cancerous tendency. In a case described by Gebhard (17) there were no signs of glandular epithelium, the tumour being composed entirely of squamous cells. The local substitution of squamous in place of another kind of epithelium is not confined to the uterus, but has been observed taking place in other organs, *e. g.* in the mouth—leucoplakia buccalis—in the conjunctiva, in pachydermia laryngis (Virchow), and in the rectum, urethra, bladder, ureters, and the pelvis of the kidney—Lichtenstern (18). It is conceivable, but unlikely, that such a process had occurred at one part of the mucous membrane in the case described above.

(2) On the other hand, a tumour in the body of the uterus, composed partly of glandular and partly of squamous cells, might arise from a metaplasia of the former into the latter, the third type of cells described above representing an intermediate stage. This view is supported by Hitschmann (*loc. cit.*), who has fully described nine cases in the uterus and one in the ovary. Gebhard (19) was not inclined to deny that such a process could take place. Although many pathologists are opposed to this, the possibility must be taken into consideration.

(3) The third possibility is in accordance with the theory originated by Cohnheim and Durante, that cancers arise from embryonal inclusions which, having never reached maturity, at some period from an unknown cause spring into activity and give rise to a malignant condition. Now, as the original epithelial elements of the Mullerian ducts form both the columnar ciliated

epithelium of the uterus and the stratified squamous epithelium of the vagina, one might assume that such embryonal elements could give rise, on the one hand, to a tumour consisting of glandular and on the other of squamous epithelial cells. One might then regard the intermediate forms described above as the direct representatives of the original embryonic cells, giving rise, on the one hand, to squamous epithelium and on the other to glandular.

(4) Finally, one must assert the possibility that, in at least some of the cases described as cancers of a double nature, the cells described as "squamous epithelium" may not in reality be such, but are merely degenerated forms of cylinder epithelium. In our case, while in many places the appearances are very strongly suggestive of a squamous-called cancer, yet, on careful consideration, one must incline to the view that the cells are not cells of another form from those of the glandular cancer, but are merely degenerated forms of these, imitating closely true squamous epithelium. In support of this are the facts that calcareous degeneration is marked throughout the tumour, that the nuclei of the so-called "squamous cells" in many cases stain very feebly, and that no true epithelial pearls are present, although structures are to be found closely resembling these. The presence of cells in cancers of the body of the uterus which resemble squamous epithelium has been drawn attention to by Cullen (20), and in two other cases of cancer of the body one has observed exactly similar appearances to those depicted by Cullen.

On these grounds, therefore, one would emphasise the possibility of mistaking degenerated forms for true squamous epithelial cells in cancers of the body of the uterus.

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May 16th, 1905.

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39. *On the nature of the vesicular structures found in malignant growths, and sometimes known as Plimmer's bodies.*

By C. E. Walker.

(With Plate III.)

De structuris vesicularibus (corporibus Plimmer ut nonnunquam appellantur) in neoplasmatibus malignis repertis.

(Cum tabulâ III.)

Summarium.

Hæc corpora, ut cognoscunt omnes, tanquam vesiculæ apparent, parietem bene definitum habentes, et vacuolum

continentes lucidum in quo granulum minutum suspendi videtur; in cellulæ cytoplasmate ad nucleum jacent; e magnitudine minutissimâ, deinde, usque ad eam nuclei ipsius variantur.

Hæc corpora (sæpe ut parasiti descripta) ego et collegæ meæ eandem structuram ortumque habere opinamur ac corpora quædam vesicularia quæ in cellulis spermatogeneticis reperiuntur.

In cellulis spermatogeneticis archoplasma per mitosis heterotypicæ prophasem, metamorphosem subiit omnino dissimilem ei quæ in cellulis somaticis accidit.

Cernuntur centrosomata extra archoplasma jacere; archoplasma ipsum vesiculatur.

Quum finditur cellula, archoplasma in cellulæ cytoplasmate inclusum evanescit; sed iterum apparet atque iterum vesiculatur per fissuræ heterotypicæ prophasem. Mitose heterotypicâ consummatâ archoplasma iterum vesiculatur, et centrosomata iterum ab eo disjunguntur.

Vesicula quæque in augendo, granulum refractivum et in sectionibus tinctis bene coloratum includere cernitur.

Vesiculæ postea aut inter se confluunt aut præter unam omnes tabescunt.

Semper autem evenit dum progreditur spermatogenesis, ut e corporibus unum, lucidum grandeque, parietem bene definitum atque granulum unum aut plura habentem, supersit. Hoc corpus in cellulis spermatogeneticis omnium animalium vertebratorum perspicuum est ac semper reperitur.

Ad nuclei ipsius magnitudinem pervenire potest, postremo fitque "pileus cephalicus" quo spermatozoon præditum est.

Hanc similitudinem fortuitam esse non putamus.

Ssimilitudines perspicuas inter cellularum figuras

mitoticas apud telam generativam et apud neoplasmata maligna anno 1903 descripsimus.

Structuræ vesiculares quas nunc describimus extra nucleum oriuntur : neoplasmatum malignorum propriæ adhuc falso æstimatæ sunt.

Non asseveramus autem telam generativam et eam neoplasmatum malignorum nihil inter se differre; similitudo tamen nunc gravior videtur.

Ambarum telarum cellulæ sine ratione cum organismi necessitatibus multiplicantur.

Ambarum telarum cellulæ nucleique, deinde, metamorphoses ostendunt quæ etsi inter se similes, valde ab eis differunt quæ in cellulis somaticis normalibus inveniuntur.

Carcinomatum cellulæ tanquam per reversionem phylogeneticam forsitan oriuntur.

In a communication to this Society last year I described certain resemblances between the cells of malignant growths and those of normal reproductive tissue observed by Professor Farmer, Mr. Moore, and myself. The points of resemblance then described were all connected with the nuclei of the cells, particularly during the processes of division.[1] In the present communication I propose to give the results of some further investigations made by my collaborators and myself, in which we have dealt with those remarkable structures known as "Plimmer's bodies."[2]

These bodies, as is well known, occur in many, if not in all, malignant growths. They appear in the form of vesicles, possessing a well-defined wall enclosing a clear space, in which are suspended one or more small darkly staining granules. They may vary in number from one to twenty or more in the same cell. They lie in the cytoplasm, commonly in close proximity to the nucleus, which they often press into a crescentic or otherwise deformed shape. In size they vary from

[1] 'Proceedings of the Royal Society,' vol. lxxii, December 8th, 1903.

[2] Plimmer, 'Practitioner,' vol. lxii.

excessive minuteness to that of the nucleus, sometimes being even larger.

These bodies are of particular interest, having been commonly regarded as peculiar to the cells of malignant growths. Many investigators have described them, and they are constantly being rediscovered. Not infrequently they have been taken for some parasitic organism, intimately connected with, if not actually causing, the disease.[1] Some observers have held that they might be degenerated centrosomes, or, at any rate, derived from them, but Benda[2] has shown that the centrosomes may co-exist independently in the cell.

Our investigations have led us to adopt an entirely different view with regard to these bodies. We are led to believe that certain vesicular structures that appear regularly during the normal development of the male reproductive elements in man and the other vertebrates are structurally identical with, and arise in a similar manner to, "Plimmer's bodies" in cancer.

A brief sketch of these vesicular structures, as found during the process of spermatogenesis, will make the reasons for the comparison between them and "Plimmer's bodies" evident.

In normal somatic or premaiotic cells the archoplasm is seen to lie beside the nucleus. In it are contained the centrosomes. In the series of metamorphoses included in the production of male sexual elements (maiotic phase), however, the archoplasm undergoes peculiar and highly characteristic changes. In 1895 Mr. Moore showed that during the prophase of the first maiotic (heterotype) mitosis the centrosomes are found to be outside of and detached from the archoplasm. At the same time the archoplasm becomes vesiculated, and eventually, at the close of this cell-generation, lost in the cytoplasm of the resulting daughter-cells. The same group of phenomena recur in the prophase of the second maiotic (homotype) division.

When the second maiotic division is over the archoplasm of the resulting cells is again seen to contain a number of minute vesicles. These continue to grow in size, each containing a single refractive and stainable granule. Then one of two things happens. Either several of these vesicles fuse together or all, excepting one,

[1] *E.g.* von Leyden, "Ueber die Parasitur des Krebeses," 'Klinischen Jahrbuch,' 1902, Weinburg?

[2] Benda, 'Verh. deutsch. gesellsch. f. Chir.,' vol. lxxiii.

atrophy. In either case the final result is the same, for there remains only one large clear body, bounded by a distinct membrane, and containing one or more darkly-staining granules.

This body, which was originally described by Mr. Moore in 1895 as the archoplasmic vesicle, is very conspicuous. It appears constantly as a peculiar feature of the spermatogenic cells of all vertebrata, and has since been encountered beyond this group by other observers. It has not been found in any normal somatic cells.

When the archoplasmic vesicle is fully developed, it frequently attains a size as large as that of the nucleus, which it presses out of shape, giving it a crescentic or otherwise deformed appearance. The vesicle and its contents eventually form the so-called "cephalic cap" of the spermatozoon.

We find, therefore, a similarity in every detail between these archoplasmic vesicles and the structures known as "Plimmer's bodies." There is also a resemblance to certain parasitic organisms, which has doubtless led to their having been so frequently described as such. In connection with this, I may, however, point out that the appearance which has apparently been interpreted as sporulation is really in the structures with which I am dealing an early stage either before the numerous small vesicles have fused together or all, excepting one, have atrophied. At any rate, the stage in which there are many is the earlier; that in which there is one is the later stage.

It hardly seems probable that this similarity in so peculiar a cytoplasmic structure, as well as the similarity in the forms of nuclear division in cancer-cells and the cells of normal reproductive tissue, can be a mere coincidence. I would, however, lay particular stress upon the fact that we do not regard the cancer-cells as identical with sexual cells. This we pointed out in our first paper dealing with malignant growths ('Proceedings of the Royal Society,' vol. lxxii, 1903), and we have never seen any reason to alter this opinion.

Nevertheless, the resemblances between what we have termed "gametoid" and the true gametogenic cells seem now to be even more significant than they did before. Both classes of cells are autonomous to a very high degree, and both possess the faculty of multiplication independently of the tissue requirements of the organism. They both, at certain stages, possess the peculiar cytoplasmic structures I have just described, and they both

exhibit nuclear metamorphoses which, in many respects, resemble one another, thus differing materially from the normal somatic cells in a similar and highly complex manner.

It seems possible that the malignant elements may be the outcome of a phylogenetic reversion, as was suggested by Sir William Collins. If this is the case, the relations between gametoid and gametogenic tissues will acquire a deeper significance. Time will not allow me, however, upon the present occasion, to discuss the possible continuance of certain ancestral characteristics in the reproductive tissues and the reversion to similar characteristics in the cells of malignant growths.

It would be out of place to deal here with Professor v. Hansemann's criticisms of my last communication to this Society, which criticism appeared recently in the 'Biologische Centralblatt,' as my collaborators and I have a paper in hand in which we treat more fully of the matter than would be permissible upon the present occasion.

We have to express our thanks to the many gentlemen who have helped us with material. I would mention Dr. Plimmer particularly, who very kindly placed some of his preparations at our disposal. *May 16th*, 1905.

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40. *On the behaviour of leucocytes in malignant growths.*

By J. E. Farmer, F.R.S., J. E. S. Moore, and C. E. Walker.

(With Plate III.)

De leucocytorum actione in neoplasmatibus malignis.

(Cum tabulâ III.)

Neoplasma malignum e cellulâ unâ oriri haud opinamur, sed e pluribus quæ habitum acquirunt malignum.

In areâ carcinomatosâ sæpe inveniuntur leucocyti in cellulis clausi.

Hoc phenomenon ut phagocytosis semper fere habetur, sed neque epithelii cellula nec leucocytus inclusus destruitur.

Multis in exemplis, utriusque cellulæ nucleum findi invenimus.

Uterque nucleus per mitosem progreditur aut apud fusos singulares aut, ut in ovi mitose primâ, cum fusis intermixtis.

Chromosomata leucocyti et epithelii cellulæ commixta, inter nucleos e mitose ortos distribui credimus. In cellulis normaliter fertilisatis, nuclei per phasem in quâ chromosomatum numerus deminuitur, jam progressi sunt, sed non adhuc probatur hoc in cellulis hic descriptis accidere.

In the present paper it is proposed to give an account of observations relating to the peculiar behaviour of leucocytes in very early examples of carcinoma occurring in various parts of the human body.

The phenomena described appear to be mainly, if not entirely, restricted to cancer in its earliest stages, and not to occur in older growths, in metastases, or in grafts introduced into other individuals. Our observations at the present moment refer more especially to: (1) a small primary rectal tumour; (2) an early case of chimney sweep's cancer, and (3) an early epithelioma of the penis. In all of these the essential details in relation to the behaviour of the leucocytes are identical, and suggest that we are here dealing with cytological phenomena peculiar to the earliest phases of the transmutation of normal tissue-cells into cancerous elements.

It has frequently been noticed that around areas that are becoming cancerous there exists a marked activity among the leucocytes, and the fact that cells in a cancerous area may contain leucocytic bodies within their cytoplasm has frequently been observed. The latter cases have been regarded generally either as phagocytic invasion of the leucocytes or as an indication that the cancer-cells have assumed a phagocytic character with respect

to the leucocytes. The results of the present investigations are not in accordance with either of these views. It was found in the rectal carcinoma above mentioned, for example (a growth that had hardly attained the size of a bean), that there was a very distinct zone of transition from the normal to the cancerous elements round the periphery of the tumour—that is to say, a zone in which it was possible to pass, within the thickness of a few cells, and almost insensibly, from elements that were merely actively dividing in the mucous layer to cells that had assumed most markedly malignant characters.

In this and other cases that we have examined we were irresistibly driven to the conclusion that the growth had not originated from a single cell, or even from a few cells, but was being evolved by the direct conversion of a great many elements definitely functioning as mucous cells into those of a truly malignant type.

Immediately within this outer zone of the tumour the leucocytic crowding was most strikingly apparent, and in a number of cells it was easy to discern the presence of leucocytes which had invaded the cytoplasm of the epithelium, where they stained readily as an inclusion. This phenomenon did not occur in the adjacent healthy tissue, and we have been unable ourselves to trace it in inflammation produced by artificial means. But the most important as well as the most singular feature about the intrusion of the leucocytes into the tumour-cells lies in the fact that neither the leucocyte nor the invaded tissue-cell appears to be injuriously affected. Neither appears to be eventually destroyed, and it was soon found that many epithelial cells that were in stages of active division contained leucocytes that had been engulphed in their cytoplasm. In many instances it was found, moreover, that while the tissue-cell was dividing mitotically, the included leucocyte was also dividing in a similar manner and at the same time. Both nuclei either passed through their mitotic evolutions upon separate spindles or the spindle figures became confused as is ordinarily the case in the first cleavage of the ovum.

It is, we think, clear from the observations just recorded that a mixture of the chromosomes derived from the leucocyte and tissue-cell respectively is distributed between the daughter nuclei resulting from the mitosis. In this way a complete disturbance of the normal chromosome constituents of the cell will be effected,

and the distribution must be of a qualitative as well as of a quantitative character. It may be well to indicate that if this process be compared to fertilisation, there exists an important difference between true gametes and the cells concerned in this anomalous fusion. In the former (gametes) we are dealing with nuclei that have passed through the phases of reduction (maiosis), whereas there is no evidence at present to show that this is so in the case now under consideration. What its relation to the ultimate

FIG. 61.

Tissue-cell, with two leucocytes lying in its cytoplasm adjacent to the nucleus.

EXPLICATIO FIGURÆ.

Cellula e carcinomate, cum duobus leucocytibus in cytoplasmate prope nucleum clausis.

reduction that does occur in neoplastic cells may be is a subject for further investigation.

It may be pointed out that the fusion here described in no way corresponds with that union which has been stated to occur between the definite cancerous cells of certain neoplastic grafts.

In bringing this brief communication to a close, we desire to express our indebtedness to the Imperial Cancer Research Fund for a grant in aid of our investigations.

July 1st, 1905.

EXPLANATION OF PLATE III,

Illustrating the communication on "The Nature of the Vesicular Structures (sometimes known as Plimmer's Bodies), found in Malignant Growths," by C. E. Walker. (P. 372.)

And the communication on "The Behaviour of Leucocytes in Malignant Growths," by J. E. Farmer, F.R.S., J. E. S. Moore, and C. E. Walker. (P. 377.)

FIG. 1.—Young spermatid of mouse, showing vesicles in the archoplasm.

FIG. 2.—A spermatid, human, further developed, containing a large vesicle.

FIG. 3.—Cell from a carcinoma of the mamma, showing appearances identical with those in Fig. 1.

FIG. 4.—Cell from a carcinoma of the mamma, showing appearances identical with those in Fig. 2.

FIG. 5.—Epithelial cell from a carcinoma, including a leucocyte. Each nucleus is in the prophase of division.

FIG. 6.—A cell similar to the preceding, showing a later phase of mitosis in each of the nuclei.

TABULA III,

Ad dissertationem "De structuris vesicularibus (corporibus Plimmer ut nonnunquam appellantur) in neoplasmatibus malignis repertis," illustrandam.

Charles Walker. (P. 372.)

Ad dissertationem insuper illustrandam "De leucocytorum actione in neoplasmatibus malignis."

J. E. Farmer, F.R.S., J. E. S. Moore, et C. E. Walker. (P. 377.)

FIGURA 1.—Muris spermatid præmaturum vesiculas in archoplasmate monstrans.

FIGURA 2.—Hominis spermatid, magis evolutum, vesiculam includens grandem.

FIGURA 3.—Cellula e mammæ carcinomate, eadem ut Figura 1 ostendens.

FIGURA 4.—Cellula e mammæ carcinomate, eadem ut Figura 2 ostendens.

FIGURA 5.—Epithelii cellula e carcinomate, leucocytum includens. Uterque nucleus in fissionis prophase.

FIGURA 6.—Epithelii cellula præcedenti similis, utriusque nuclei mitose magis progressâ.

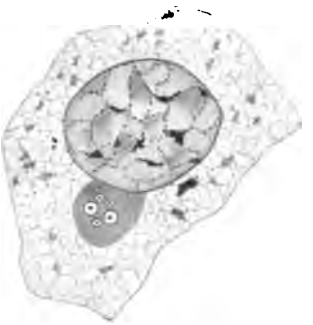


Fig. 1.

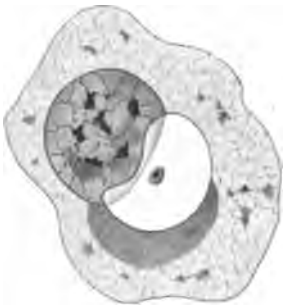


Fig. 2.

Fig. 3.

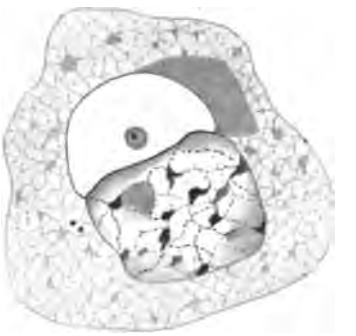


Fig. 4.

Fig. 5.

Fig. 6.

Lith. Anst. v. F. A. Funke, Leipzig

41. *The rôle of the lymphocyte.*

By J. Burton Cleland.

From the Pathological Institute, London Hospital.

The *rôle* of the lymphocyte in the economy of the body is still a much discussed question, and, as yet, no finality has been attained. During the course of a close study into the cytology of the germ-centres of lymphatic glands a view has presented itself which seems to explain satisfactorily certain anomalous points. This view will first be briefly propounded and then the evidence in favour thereof more fully set forth.

The lymphocytes are formed in special organs, the germ-centres of lymphatic glands, the rest of the "glandular" tissue representing a storehouse of these elaborated cells. The large cells constituting the centres, by a process analogous to the conversion of a spermatid into a spermatozoon, become eventually ordinary lymphocytes. This differentiation serves a definite purpose—the easy passage of the cells through narrow channels throughout the body. During their course through the circulating fluids the part they play is entirely passive, and they have no active functions to perform. When certain irritants, chemical or mechanical, lodge in the tissues, these cells are arrested in their onward progress along the narrow vessels in the neighbourhood and rapidly accumulate. A process of reconstruction now takes place in these collected lymphocytes, and they assume again many of the characters that they originally possessed in the germ-centre, amongst others that of proliferation. These cells are now variously styled "round connective-tissue cells," "endothelial cells," the "epithelioid" cells of a tubercle formation, etc., though it must be remembered that true connective tissue and endothelial cells are also present and also proliferate. The result is a mass of granulation tissue, the cells of which may be further modified into plasma cells, fibrous tissue cells, mast cells, and the various constituents of organising tissue.

The view adopted, in fact, is this: A special organ furnishes a constant supply of lymphocytes to the blood, and these cells can be accumulated with very great rapidity at any particular point where rapid cell-proliferation may be necessary to protect the individual from some extraneous attack. The rapidity with

which a protective barrier may thus be raised is much greater than if entire reliance had to be placed on the "fixed" cells of the part. If these latter cells were in any degree specialised, say into the cells of fibrous tissue, they would first have to undergo retrograde changes to a certain extent before they could divide by mitosis, a proceding which would mean the loss of much valuable time.

The support given to this view may be considered from three standpoints, viz.: (1) The origin and specialisation of

FIG. 62.

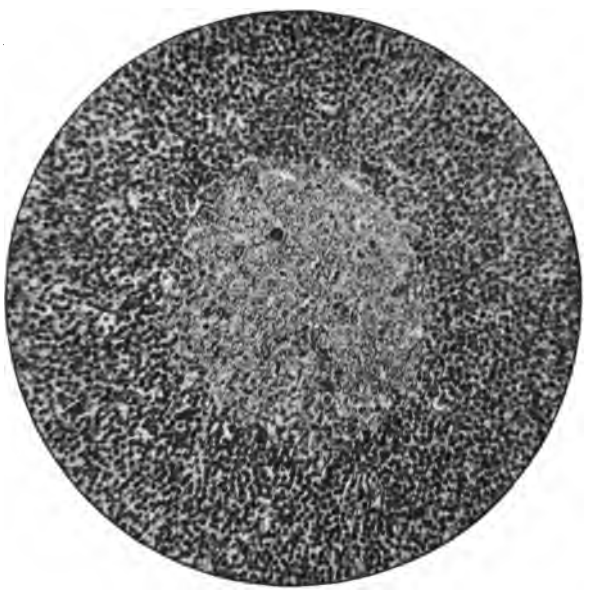
Enlarged germ-centres in a cervical lymphatic gland from a child.

the lymphocyte; (2) the characters presented by it as a free cell in the blood; and (3) the evidence in favour of its active participation in the formation of organising tissue.

(1) *The origin and specialisation of the lymphocyte.*—The "germ-centres" of lymphatic glands are commonly considered as the "breeding-ground" of the lymphocytes. In examining sections of normal glands, very few mitotic figures will be observed apart from these areas. Occasionally one will be encountered, but as all cells in the body, except from the point of view of size, resemble each other closely during indirect division, and as all individual peculiarities are lost while this is

in progress, it is impossible to say whether the cells so dividing are really lymphocytes, or the endothelial and connective-tissue cells of the supporting stroma, or endothelioid cells of very small germinal areas. Their number is practically insignificant, however. In chronic inflammatory changes—lymphadenoma, etc.—such figures, occurring undoubtedly in the supporting tissues, are more numerous. The only likely places in the lymphatic glands, then, for the manufacture of so many cells as are found in these organs are the germ-centres. These areas are said to be

FIG. 63.

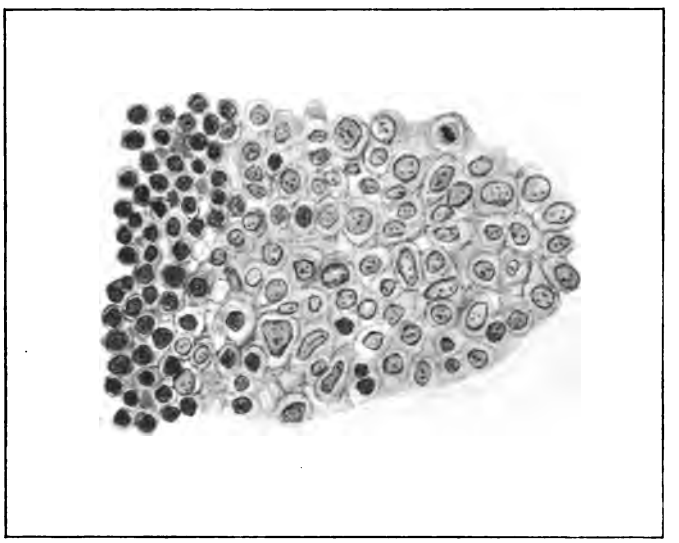


Germ-centre in an axillary lymphatic gland. From this the figure following was made.

most conspicuous in childhood and to grow smaller, and finally almost disappear, as old age is reached. They are sometimes small, at others indistinct and diffuse, but occasionally are very large and conspicuous objects, showing rapid proliferation amongst their cells; in one of these cases I have counted as many as twenty-seven division figures in one field of a $\frac{1}{12}$-inch oil immersion lens. In such an area, fixed in Flemming's solution immediately after removal on the operating-table and stained with safranin, gentian-violet, and Orange G, may be traced the transition from the large endothelioid cells with large

vesicular nuclei in the centre of the patch, to others in which the protoplasm was less and the nucleus more condensed, and, finally, at or near the periphery, these latter into cells only differing from lymphocytes in possessing a little more protoplasm and a little less densely aggregated chromatin in the nucleus. The last-named, arranged concentrically at the circumference of the area, pass insensibly into and mix with the numerous lymphocytes, likewise concentrically arranged round the area.

FIG. 64.



The edge of the germ-centre shown in the preceding figure. The "centre" lies on the right-hand side, the lymphocytes produced from it, on the left. × 667.

Here, then, is a direct transformation of large endothelioid cells into others indistinguishable from lymphocytes. Since lymphocytes are not met with in the centres of these large areas, it would seem that the cells in this position represent the mother-cells of the lymphocytes, and are continuous as such; and that the daughter-cells divide and divide, and their offspring are pushed towards the periphery, where they gradually undergo the transformation above described. This origin for the lymphocytes is, of course, well recognised, but I wish to draw particular

attention to the specialisation of the cells, after division, into lymphocytes.

A somewhat similar conversion of cells for a definite purpose—that of transit through a fluid medium—is seen in the formation of spermatozoa from spermatids, though there is in this instance a further differentiation of structure to enable the cell to be actively motile and to pierce the wall of the ovum. The spermatid, as first formed, is a large cell with much protoplasm and a conspicuous vesicular nucleus. Gradually the protoplasm diminishes in size—part, in fact, is extruded from the cell—and the nuclear chromatin condenses. Finally, in the spermatozoon the protoplasm has almost reached the vanishing point and the chromatin is condensed into a wonderfully small compass. The cell, from its small size, is now perfectly fitted for travelling quickly through a fluid medium. Having entered the ovum, the small, densely chromatic nucleus begins to expand again, and may even, in some instances, form a large vesicular male pro-nucleus before conjugating with the female.

This last point, the return of the nucleus to its previous large vesicular condition, at once suggests the possibility of a similar return of the whole cell in the lymphocyte to a condition resembling its original state, should it be subjected to the necessary condition. The requisite condition seems to be the arrest of the cells in any particular tissue through the influence of some irritant present in that tissue.

Before leaving the discussion of the germ-centres, it should be mentioned that certain of the "large lymphocytes" and "hyaline cells" of the blood may be accounted for by the escape of cells from the germ-centres before their complete conversion into lymphocytes. Cells from these areas somewhat closely resemble the varieties of leucocytes in question.

(2) *Characters presented by the lymphocyte as a free cell in the blood.*—On examining the free cells circulating in the blood, we can, from their general appearance, gather some information as to their probable functions. An examination of the red cell, for instance, discloses at once the fact that its office is that of a hæmoglobin carrier. The polymorphonuclear leucocyte, again, is seen to be phagocytic; moreover, its nucleus is much lobed, and presents a very large superficies to the cytoplasm in consequence. As such a much-divided nucleus seems often associated

with great secretory activity,[1] it is possible that metabolic processes of this nature are some of the most important duties of these cells, the products being perhaps certain of the anti-bodies associated with bacterial invasions. When we come to the lymphocyte, however, the third most numerous cell in the blood, we find a structure distinctly different from either of the first two. Its cytoplasm is so reduced in amount that there is no room left for holding any substance, such as hæmoglobin, or for engulphing foreign bodies and organisms, as in phagocytosis. This small amount of cytoplasm, associated with a small spherical nucleus of densely-packed chromatin, is also an argument against any great secretory activity on the part of the cell. As seen in the circulating blood, in fact, its appearance suggests a passive cell with no active function which we can, with any likelihood, attribute to it. But this very appearance, though antagonistic to any active duties to be performed, is one eminently suited to fulfil quite another purpose. The lymphocyte is one of the smallest cells in the body, its cytoplasm is very much reduced in amount, and its nucleus is contracted in such a manner that the chromatin is bunched together into a dense mass. In other words, all its structures are reduced to as small a compass as possible, and the figure thus assumed is spherical. These are properties which allow the body possessing them to travel with great ease in the circulating fluid in which it lies. The spherical shape is one that permits of a rolling and disengaging action should the circumference of the sphere at any point touch the wall of the vessel and tend to be retarded in its course, and the small size enables the cell to be carried through minute capillaries, lymph-spaces, and lymph-vessels, at the mouths of which the larger cells of the blood would be debarred entrance. We see, then, in the lymphocyte a cell eminently fitted for easy and rapid conveyance throughout the whole vascular and lymphatic systems, even when these passages are exceedingly narrow, and it may easily be understood how quickly they will accumulate at any particular point should changes in the vessel-walls, the result of irritation, "filter" them, as it were, from the circulating fluids in that part.

(3) *Evidence in favour of the lymphocyte participating in the formation of organising tissue.*—Various observers have, at

[1] Wilson, 'The Cell,' p. 348

different times, satisfied themselves that lymphocytes may be converted into cells like those of the "fixed cells" of an irritated part, and may then proceed to organisation. Thus Dr. Mott F.R.S., at the recent meeting of the British Medical Association at Leicester, figured all the stages in the conversion of lymphocytes into plasma cells. I have myself traced the passage of the latter into fibrous tissue cells. Again, Miller, in the 'Journal of Pathology and Bacteriology' for November, 1904, describes a similar conversion into fixed cells in his account of the histogenesis of the tubercle. He points out that, within a few hours of the injection of tubercle bacilli into the blood of the portal vein in rabbits and their arrest in the liver, numerous lymphocytes surround these foreign bodies, and that all gradations from lymphocytes to the typical "epithelioid" cells of the tubercle can be traced. In fact, he does not hesitate to attribute the formation of some, if not all, of these epithelioid cells to this source. The *rôle* of the lymphocytes in the last instance cannot be an isolated one, confined to tubercle, but must be considered of general import and as an indication of what occurs, with various modifications, under all similar conditions. We know how hard it often is, in chronic inflammatory states, to decide whether particular cells are to be considered as escaped lymphocytes arrested in the part or as small round connective-tissue cells. Under this view we see that there is really no absolute difference between the two, and that the lymphocyte is merely a modified connective-tissue cell which can be carried to any particular point in great numbers, and in a short space of time, to reinforce the fixed cells there, and to play a similar part in organisation. The lymphocytes represent a reserve of cells which are of great importance, especially when the part irritated is one very poor in cells—for instance, dense fibrous tissue—in which, in consequence of their small numbers, the fixed cells can play but a slow and subordinate part in contributing to the number of inflammatory cells.

It seems to me that only by some theory such as the one propounded can we explain the presence in the blood of such an anomalous cell as the lymphocyte. Its occurrence in such constant numbers in normal blood indicates that it is more than merely washed accidentally into the blood-stream.

The lymphocytes and lymphatic glands.—The unstriped muscle-

fibre found in small amount in the capsule of lymphatic glands will, when it contracts, not only force on the lymph into the lymphatic vessels, but will also squeeze out with this a certain number of lymphocytes. The number of these thus escaping will vary with the degree and frequency of contraction of the muscular fibres. Their place will be taken by the continual output from the germ-centres. During digestion the activity of the mesenteric glands is great; many lymphocytes being thus squeezed into the circulation, we have a "digestive lymphocytosis." A false lymphocytosis may arise in this way—false in that the number of these cells in the body is not increased but only their number in the blood, and with this is a corresponding fall in the number in the lymphatic tissues. Various toxins cause unstriped muscle-fibres to contract; such may exert their influence on these structures in the lymph-glands, causing more frequent or more prolonged contractions of these organs and so increasing the number of lymphocytes in the circulating fluids. Thus is accounted for the lymphocytosis met with in a few diseases, but this is not necessarily associated with increased mitotic activity in the germ-centres.

These observations have cropped up as a bye-issue during an investigation carried out at the London Hospital into the cytology of malignant growths; the frequency of division figures in the germ-centres and certain unusual features in them arrested attention and led to a close examination of a number of sections of these organs. The view that I have suggested followed as a natural conclusion, and, considering the present ambiguity of the subject, seemed worthy of mention as a possible explanation of what appeared otherwise obscure.

Finally, I would like to express my thanks to Dr. Otto Grünbaum for his kindly criticism and suggestions.

1905.

INDEX.

SUBJECTS.

(*For List of Authors see p.* 391.)

PAGE

ADRENAL, relation of, to the sexual organs (W. Bulloch and J. H. Sequeira) 189

ADRENAL, tumour of, associated with precocious sexual development (C. E. Adams) 208

ALIMENTARY CANAL, sarcomata of the (E. M. Corner and H. A. T. Fairbank) 20

AMPULLA OF VATER, cyst in connection with (R. S. Trevor) . . 138

ARTERITIS, OBLITERATIVE (W. P. S. Branson) . . . 212

„ — — (E. Michels and F. P. Weber) 223

BACILLUS ENTERITIDIS, in cow's milk (E. Klein) . . . 132

BACILLUS PESTIS, acid media in isolation of (W. C. C. Pakes and F. H. Joseph) 135

BACILLUS TYPHOSUS, the vitality of, in shell-fish (E. Klein) . . 231

BONE, secondary osteoplastic carcinomatosis of (F. H. Thiele) . . 314

BRONCHO-PNEUMONIA with multiple cavities (J. M. Bernstein) . 330

CALCULUS, a prehistoric Egyptian (S. G. Shattock) . . . 275

CALCULUS, PHOSPHATIC, formed on an ear of wheat-straw, in a male (W. H. Battle) 296

CARCINOMA: see *Tumour*.

CARDIA, carcinoma of, involving œsophagus (J. Fawcett) . . 259

CASTRATION AND VASECTOMY, the results of, upon the prostate gland in the enlarged and normal condition (C. S. Wallace) . . . 80

COMPARING ABNORMAL WITH NORMAL TISSUES beneath the microscope, methods of (S. G. Shattock and C. F. Selous) . . 53

FILARIAL AND MALARIAL PARASITES, simultaneous occurence of, in the blood (C. F. Selous) 113

FUGENT, a new stain (F. H. Joseph) 137

GANGRENE, EMPHYSEMATOUS (L. S. Dudgeon and P. W. G. Sargent) . 42

GASTRIC CONTENTS, chemical examination of, for active hydrochloric acid (W. H. Willcox) 250

HEAT REGULATION of the body, a research into, by means of an investigation of death temperatures (E. M. Corner and J. E. H. Sawyer) .

HYDROCHLORIC ACID, active, examination of gastric contents for (W. H. Willcox) 250

PAGE

JAUNDICE, TOXÆMIC (J. F. H. Broadbent) 145

LIVER, a case of subacute atrophy of (S. G. Scott) . . . 298
LUNG, unusual form of consolidation, occurring in a case of occlusion of bronchus by blood-clot (T. J. Horder) 106
LYMPHOCYTE, the *rôle* of the (J. B. Cleland) . . 381
LYMPHOCYTHÆMIA, ACUTE (L. S. Dudgeon) . . . 114

MALFORMATION of the lower extremities (H. Rundle) . . 307
MYASTHENIA GRAVIS (E. F. Buzzard) 355

OPSONIC CONTENT of the blood-serum, variations in health and in cases of lupus (W. Bulloch) 334

PROSTATE GLAND in the enlarged and normal condition, the results of castration and vasectomy upon (C. S. Wallace) . . . 80
PROTEID CHEMISTRY. recent work on (W. D. Halliburton) . . 158

SARCOMA: see *Tumour*.
SCHISTOSOMA CATTOI (J. Catto) 179
SEXUAL CHARACTERS, secondary or external, results of vasectomy and castration upon the appearance of (S. G. Shattock and C. G. Seligmann) 57
SEXUAL ORGANS, relation of adrenals to (W. Bulloch and J. H. Sequeira) 189
SMALLPOX, VACCINIA, AND VARICELLA, parasites of (W. E. De Korté) 172
STIMULINS, some experiments in connection with (W. B. Leishmann) . 344

TEMPERATURE, a research into the heat regulation of the body by means of an investigation of death temperatures (E. M. Corner and J. E. H. Sawyer) 1
THYMUS, experiments on the grafting of, in animals (L. S. Dudgeon and A. E. Russell) . . . . . .
TUMOUR, carcinoma, etiology of (K. W. Monsarrat), with report of committee 262
„ the nature of the vesicular structures found in malignant growths, and sometimes known as Plimmer's bodies (C. E. Walker) . . 372
„ on the behaviour of leucocytes in malignant growths (J. E. Farmer, J. E. S. Moore, and C. E. Walker) 377
„ cyst, in connection with ampulla of Vater (R. S. Trevor) . . 138
„ sarcomata of alimentary canal (E. M. Corner and H. A. T. Fairbank) . 20
„ carcinoma of adrenal, associated with precocious sexual development (C. E. Adams) 208
„ carcinoma of cardia, involving œsophagus (J. Fawcett) . . 259
„ carcinoma, secondary, osteoplastic, of bone (F. H. Thiele) . . 314
„ carcinoma, squamous-celled, of finger, associated with exposure to X rays (A. G. R. Foulerton) 327
„ carcinoma of body of uterus, with squamous epithelium in (R. D. Keith) 365
TYPHOID FEVER, suppurative periostitis following (W. H. Battle and L. S. Dudgeon) 291

VASECTOMY AND CASTRATION, results of, upon the appearance of secondary or external sexual characters (S. G. Shattock and C. G. Seligmann) 57

X RAYS, carcinoma of finger, associated with exposure to (A. G. R. Foulerton) 327

AUTHORS.

PAGE

ADAMS (C. E.), a case of precocious development associated with a tumour of the left supra-renal body 208

BATTLE (W. H.) and **DUDGEON** (L. S.), suppurative periostitis following typhoid fever 291

BATTLE (W. H.), a phosphatic calculus formed on an ear of wheat-straw in a male 296

BERNSTEIN (J. M.), broncho-pneumonia with multiple cavities . . 330

BRANSON (W. P. S.), obliterative arteritis 212

BROADBENT (J. F. H.), toxæmic jaundice and interstitial hepatitis . 145

BULLOCH (W.) and **SEQUEIRA** (J. H.), on the relation of the supra-renal capsules to the sexual organs 189

BULLOCH (W.), variations in the opsonic content of the blood-serum in health and in cases of lupus 334

BUZZARD (E. F.), myasthenia gravis 355

CLELAND (J. B.), the *rôle* of the lymphocyte 381

CORNER (E. M.) and **SAWYER** (J. E. H.), a research into the heat regulation of the body by means of an investigation of death temperatures 1

CORNER (E. M.) and **FAIRBANK** (H. A. T.), sarcomata of the alimentary canal, with report of a case 20

CATTO (J.), Schistosoma cattoi: a new blood fluke of man . . 179

DE KORTÉ (W. E.), the parasites of smallpox, vaccinia, and varicella . 172

DUDGEON (L. S.) and **SARGENT** (P. W. G.), two cases of emphysematous gangrene due to the *Bacillus aerogenes capsulatus* 42

DUDGEON (L. S.), acute lymphocythæmia 114

DUDGEON (L. S.) and **RUSSELL** (A. E.), experiments on the grafting of the thymus gland in animals 238

DUDGEON (L. S.): see *Battle, W. H.*

FAIRBANK (H. A. T.): see *Corner, E. M.*

FARMER (J. E.), **MOORE** (J. E. S.), and **WALKER** (C. E.), on the behaviour of leucocytes in malignant growths 377

FAWCETT (J.), carcinoma of the cardiac orifice of the stomach, involving the œsophagus 259

FOULERTON (A. G. R.), squamous-celled carcinoma of the finger associated with exposure to X rays 327

HALLIBURTON (W. D.), recent work on proteid chemistry . . 159

HORDER (T. J.), an unusual form of consolidation of left lung occurring in a case of occlusion of bronchus by blood-clot . . . 106

JOSEPH (F. H.), Fugent—a new stain 137

„ see *Pakes, W. C. C.*

KEITH (R. D.), on the occurrence of squamous epithelium in carcinoma of the body of the uterus. 365

KLEIN (E.), the occurrence of *Bacillus enteritidis* (Gaertner) in cow's milk 132

„ the vitality of the typhoid bacillus in shellfish . . . 231

PAGE

LEISHMAN (W. B.), some experiments in connection with stimulins . 344

MICHELS (E.) and **WEBER** (F. P.), obliterative arteritis, leading to gangrene of extremities in otherwise apparently healthy men in the prime of life 223

MONSARRAT (K. W.), the etiology of carcinoma . . . 262

MOORE (J. E. S.) : see *Farmer, J. E.*

PAKES (W. C. C.) and **JOSEPH** (F. H.), a note on the use of acid media in the isolation of *B. pestis* 135

RUNDLE (H), a case of asymmetrical congenital malformation of the lower extremities 307

RUSSELL (A. E.) : see *Dudgeon, L. S.*

SARGENT (P. W. G.) : see *Dudgeon, L. S.*

SAWYER (J. E. H.) : see *Corner, E. M.*

SCOTT (S. G.), a case of subacute atrophy of the liver . . . 298

SELIGMANN (C. G.) : see *Shattock, S. G.*

SELOUS (C. F.), the simultaneous occurrence of filarial and malarial parasites in the blood 113

„ see *Shattock, S. G.*

SEQUEIRA (J. H.) : see *Bulloch, W.*

SHATTOCK (S. G.) and **SELOUS** (C. F.), two methods of comparing normal with abnormal tissues beneath the microscope . . . 53

SHATTOCK (S. G.) and **SELIGMANN** (C. G.), observations upon the acquirement of secondary sexual characters, indicating the formation of an internal secretion by the testicle 57

SHATTOCK (S. G.), a prehistoric Egyptian calculus . . . 275

THIELE (F. H.), secondary carcinomatosis of bones and osteoplastic changes connected with them 314

TREVOR (R. S.), an intra-intestinal cystic swelling in connection with the ampulla of Vater 138

WALKER (C. E.), on the nature of the vesicular structures found in malignant growths, and sometimes known as Plimmer's bodies . 372

„ see *Farmer, J. E.*

WALLACE (C. S.), the results of castration and vasectomy upon the prostate gland in the enlarged and normal condition . . . 80

WEBER (F. P.) : see *Michels, E.*

WILLCOX (W. H.), the chemical examination of the gastric contents, with an accurate clinical method of determining the active hydrochloric acid present 250

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